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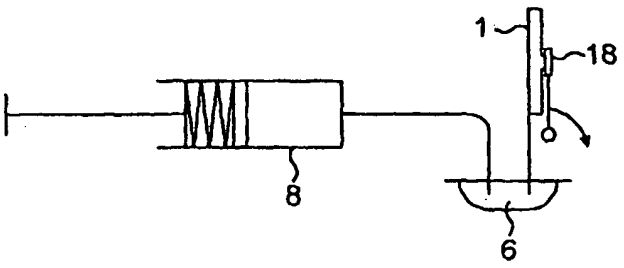

(57) Abstract: An inhaler for producing an inhalable aerosol of a powdered medicament includes a pump 8 in fluid communication with a drug entrainment device 6 and an aerosolising device 1. A valve 18 is provided at the exit of the aerosolising device so that the whole fluid system can be pressurised before the valve 18 is opened to allow air flow to entrain and aerosolise the powdered medicament. The inhaler allows efficient aerosolisation of a powdered medicament using a smaller volume of air.

Inhalers

BACKGROUND OF THE INVENTION

The present invention relates to inhalers and in particular inhalers for the delivery of a medicament to the lung, more particularly a medicament in powder form.

In recent times, there has been a growing interest in the systemic delivery of pharmaceutically-active medicaments via the lung. Such a method of delivery is generally more attractive to the patient than methods such as injection, because it does not involve a needle and can be carried out discreetly in public.

For a medicament in a particulate form the provision of an inhalable aerosol requires an inhaler that can produce a repeatable dose of fine particles. In order for the particles of medicament to reach the lung and thus be absorbed into the bloodstream, the particles must have an effective diameter in the range of approximately 1 to 3 microns. The portion of the emitted aerosol within this range of particle size is known as the "fine particle fraction". If the particles are larger than 5 microns they may not be transported by the inhaled airflow deep into the lung, because they are likely to be trapped in the respiratory passages before reaching the deep lung. For example, particles of the order of 10 microns are unlikely to progress further than the trachea and particles of the order of 50 microns tend to deposit on the back of the throat when inhaled. Furthermore, if the particles are less than 1 micron in effective diameter, the particles may not be absorbed in the lung, because they are small enough to be expelled from the lung with the exhaled airflow.

Thus, it will be seen that it is important that a powdered medicament is delivered with an accurately controlled range of particle size in order that it is absorbed effectively in the lung.

In traditional metered dose inhalers (MDIs) it is common for the emitted dose (the amount of medicament that enters the patient's airway) to be around 80 to 90% of the nominal dose in the inhaler. The fine particle fraction may be only around 50% of the emitted dose. However, the variation in the fine particle fraction of known inhalers can be ± 20 to 30%. Such variation may be acceptable in the case of asthma drugs and the like, but when the medicament is a more potent drug such as insulin, growth hormone or morphine, this amount of variability in the dosing is unacceptable. The relatively low fine particle fraction also represents a significant wastage of what may be an expensive drug. Furthermore, there may be side effects if the proportion of the emitted dose which is not respired is swallowed.

Thus, it is important for the systemic delivery of medicaments by inhalation that a repeatable dose of fine particles can be produced.

WO 90/15635 describes a device for the pulverisation of particles or agglomerates of a powdered inhalation medicament comprising a rotationally symmetrical vortex chamber with spaced inlet and outlet ports. The inlet port directs air inflow into the vortex chamber substantially parallel to the tangent of the chamber. In one arrangement the chamber has a central outlet port. According to this document the optimum diameter of a vortex chamber operating by the action of inhalation is 10-20 mm. A cylinder with a diameter of 4 mm is disclosed for use with a source of pressurised air.

WO 01/00262 discloses an inhaler comprising a pump, a drug dosing device and a cyclone, which delivers an aerosol of powdered medicament from the drug dosing device into a chamber when the pump is activated. The aerosol is inhaled by the user through a mouthpiece. The cyclone comprises a cylindrical chamber with an axial outlet and a tangential inlet. The cyclone has a

preferred diameter between 4 and 10 mm.

Particles of medicament can be separated by generating shear forces between the particles, for example by providing a substantial velocity gradient across the particles. This may be done, for example, by forcing the powder through a narrow nozzle at high speed, for example as described in WO 93/00951, or introducing the powder into a turbulent air stream. Alternatively, a cyclone of the type described in WO 01/00262 can be used.

It is known for so-called "spacers" to be used in the generation of the aerosol from a metered dose inhaler. The spacer fits onto the mouthpiece of the inhaler and comprises a chamber into which the dose of medicament is ejected by the inhaler. The patient is then able to inhale the dose from the spacer through a corresponding mouthpiece on the spacer. Such spacers retain a fast-moving aerosol ejected from the inhaler, and hold it until it can be inhaled by the user. However, a proportion of the particles in the aerosol will be retained on the walls of the spacer which makes it difficult to predict reliably the dose of medicament that the user inhales. Furthermore, the larger size of the spacer makes the inhaler more cumbersome and less discreet.

SUMMARY OF THE INVENTION

The present invention, at least in its preferred embodiments, seeks to provide an inhaler which is capable of reliably generating an inhalable aerosol of a powdered medicament with an effective particle size that is sufficiently small for the medicament to be delivered to and absorbed in the lungs of a patient.

According to the present invention, there is provided an inhaler for producing an inhalable aerosol of a powdered medicament, the inhaler comprising:

a drug entrainment device for entraining a powdered

medicament in a gas flow;

a gas source arranged to supply pressurised gas to the drug entrainment device; and

a valve which is selectively actuable to prevent gas flow through the drug entrainment device,

wherein the drug entrainment device is located in a flow path between the gas source and the valve.

Thus, according to the invention a valve is provided downstream of the drug entrainment device relative to the gas source. The valve is able to prevent gas flow through the drug entrainment device. In this way, the gas source can be activated while the valve is closed to pressurise the flow path through the drug entrainment device. Once the flow path through the drug entrainment device has been pressurised, the valve can be opened to allow gas flow through the inhaler, including the drug entrainment device, to generate the aerosol.

The inventors have found that an inhaler which is configured to operate in this way requires a significantly smaller volume of air to achieve the required aerosolisation of a dose of dry powdered medicament. Furthermore, it has been found that an inhaler configured and operated in this way is less likely to suffer from a build-up of medicament from previous deliveries in the fluid system.

The provision of a valve downstream of the drug entrainment device allows the pressure in the drug entrainment device to be raised to the required level before there is any gas flow. In this way, the required pressure can be achieved without any significant flow of gas from the gas source. Without the valve, the necessary pressure must be achieved while gas is flowing so that an amount of gas is wasted in bringing the fluid system to the required operating pressure. In accordance with the invention, the operations of pressurising the inhaler fluid system and generating gas

flow through the inhaler fluid system can be carried out separately.

The pressurisation of the drug entrainment device before the gas is allowed to flow allows gas between agglomerated particles of medicament in the drug entrainment device to become pressurised. When the valve is opened the gas between the particles expands suddenly and thereby assists in breaking up the agglomerated particles of medicament. In this way, the powdered drug is also fluidised which makes it easier to move.

Furthermore, the increase in pressure of the gas in the drug entrainment device causes a proportional increase in the density of the gas. The denser gas is able to carry particles of medicament more easily and will therefore entrain the drug more effectively.

The gas source may be a compressed air line or other similar source of pressurised gas. However, this is not preferred as it is desirable for the inhaler to be self-contained. Consequently, the gas source may comprise a canister or reservoir of pressurised gas. The canister may be rechargeable, for example by means of a pump.

The gas source may comprise a pump for providing a gas flow to the drug entrainment device. A pump has the advantage that it does not require recharging or replacing in the manner of a gas canister. The pump may be in any suitable form, for example a squeeze bulb, a bellows pump or such like. A preferred type of pump is a piston pump and reservoir. The piston pump may comprise a plunger received in a pump cylinder. The pump may be arranged to charge a gas reservoir, for example by the plunger compressing gas in the pump cylinder. Preferably, the reservoir is charged by one stroke of the piston. The reservoir may be formed by part of the pump cylinder.

The inhaler may comprise a first gas source

arranged to supply pressurised gas to the drug entrainment device at a first pressure and a second gas source arranged to supply pressurised gas to the drug entrainment device at a second pressure. The second pressure may be greater than the first pressure. According to such an arrangement, the higher pressure gas from the second gas source may be used initially to fluidise the drug or later to scour the fluid pathways.

The first gas source and the second gas source may comprise respective piston pumps having different diameters.

The inhaler may comprise a breath-actuation device which is arranged to actuate the valve or the pump, canister or other source of pressurised gas when the user inhales. The mouthpiece may comprise the breath-actuation device.

The drug entrainment device may comprise a substantially cylindrical entrainment chamber having a substantially tangential inlet. The entrainment chamber may also comprise a substantially tangential outlet spaced axially from the inlet.

In one preferred arrangement, the drug entrainment chamber may be in the form of a drug capsule, such as a blister or other disposable package. The drug capsule may be punctured in use to provide the necessary fluid passages for drug entrainment. In a preferred arrangement, the drug entrainment chamber is in the form of a foil blister with a flat lid.

The valve may be arranged to be manually actuated by the user. Alternatively, the valve may be actuated in response to a level of pressure generated by the gas source. In this way, when the medicament in the drug entrainment device is pressurised to the desired level, the valve is actuated to allow gas flow through the drug entrainment device. The valve may be actuated in response to a signal from a pressure sensor. Preferably, however, the valve is actuated directly by

the pressure generated by the gas source.

In a preferred embodiment, the valve is actuated by a breath actuation device in response to the inhalation of the user.

The inhaler may comprise a further valve located in a flow path between the gas source and the drug entrainment device. The further valve may be arranged to control flow from the gas source so that it is unnecessary for the first valve to control the gas flow for extended periods of time.

In a particularly convenient configuration, the valve (or valves) comprise a membrane which is arranged to be punctured to open the valve. In this way, the membrane of the valve can form part of a disposable component of the inhaler. In particular, the membrane may close a drug capsule which contains at least one dose of powdered medicament. The drug capsule may comprise a drug entrainment chamber of the drug entrainment device. The drug capsule may be in any suitable form and in a preferred configuration, the drug capsule is in the form of a blister, for example a cold formed foil blister.

The inhaler may comprise an aerosolising device. The aerosolising device may comprise the drug entrainment device. For example, the drug entrainment device may also be an aerosolising device. The drug entrainment device may be arranged to entrain and aerosolise the drug in a single operation.

The aerosolising device may be located in a flow path between the drug entrainment device and the valve. In this case, the drug entrainment device and the aerosolising device can both be pressurised by the gas source while the valve is closed.

Alternatively, the valve may be located in a flow path between the drug entrainment device and the aerosolising device. In this case, the drug entrainment device can be pressurised by the gas source without

pressurisation of the aerosolising device. In this arrangement, therefore, while the entrained powder passes through the valve, it is unnecessary for the finely divided aerosolised medicament to pass through the valve. This arrangement reduces the likelihood of powder deposition around the valve.

The aerosolising device may be in any suitable form, for example, the aerosolising device may be in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial exit port. In this case, the aerosolising device of the inhaler is arranged such that a flow of gas entering the vortex chamber through the inlet port is guided in a rotating path until it leaves the vortex chamber via the exit port. The exit port is generally aligned with the axis of the rotation of the gas flow. When a powdered medicament is entrained in the gas flow, shear forces due to the velocity gradient in the boundary layer adjacent the wall of the vortex chamber break up the agglomerated particles of medicament to form an aerosol of fine particles.

The inlet port can be considered as the end portion of an inlet conduit through which a gas flow enters the vortex chamber, in use. Similarly, the exit port can be considered as the beginning portion of an exit conduit through which the gas flow exits the vortex chamber, in use. An axial exit port directs the gas flow out of the vortex chamber in a substantially axial direction or with a substantial component in the axial direction.

The terms "axial", "radial" and "tangential" are used herein to define the geometry of the vortex chamber. These terms are best understood by reference to the vortex formed within the vortex chamber in use. Thus, the axial direction is a direction parallel to the axis about which the vortex rotates. The radial direction is a direction outward from the axis about

which the vortex rotates. The tangential direction is a direction parallel to the instantaneous direction of motion of a particle in the vortex. Consequently, it is not necessary for the vortex chamber to have a perfectly circular cross-section, and the vortex chamber need only be sufficiently circular to form an effective vortex. It is desirable for the perimeter of the vortex chamber to form a smooth curve, as it has been found that an angular perimeter can lead to deposition of the medicament in the vortex chamber.

The ratio of the diameter of the vortex chamber to the diameter of the exit port can be significant in maximising the fine particle fraction of the medicament aerosol which is expelled from the exit port. Thus, the ratio of the diameter of the vortex chamber to the diameter of the exit port may be between 4 and 12. It has been found that when the ratio is between 4 and 12 the proportion of particles of the powdered medicament with an effective diameter in the range 1 to 3 microns is maximised. For an enhanced fine particle fraction, the ratio is preferably greater than 5, most preferably greater than 6 and preferably less than 9, most preferably less than 8. In the preferred arrangement, the ratio is 7.1.

In embodiments of the invention, the diameter of the vortex chamber is between 2 and 12 mm. The diameter of the vortex chamber is preferably greater than 4 mm, most preferably at least 5 mm and preferably less than 8 mm, most preferably less than 6 mm. In the preferred embodiment, the diameter of the vortex chamber is 5 mm.

In embodiments of the invention, the height of the vortex chamber is between 1 and 8 mm. The height of the vortex chamber is preferably less than 4 mm, most preferably less than 2 mm. In the preferred embodiment, the height of the vortex chamber is 1.6 mm.

In general, the vortex chamber is substantially cylindrical. However, the vortex chamber may take other

forms. For example, the vortex chamber may be frustoconical. Where the diameter of the vortex chamber or the exit port is not constant along its length, the ratio of the largest diameter of the vortex chamber to the smallest diameter of the exit port should be within the range specified above.

The aerosolising device comprises an exit port, for example as described above. In embodiments of the invention, the diameter of the exit port is between 0.5 and 2.5 mm. The diameter of the exit port is preferably greater than 0.6 mm and preferably less than 1.2 mm, most preferably less than 1.0 mm. In the preferred embodiment, the diameter of the exit port is 0.7 mm.

The exit port may comprise a plurality of apertures or passageways. In this case, the diameter of the exit port is considered as the diameter of the smallest circle which circumscribes all of the apertures or passageways which form the exit port.

The inhaler may comprise an exit conduit through which the medicament aerosol passes after leaving the aerosolising device. The exit port may form part of the exit conduit nearest the aerosolising device. If the exit conduit is short, the exit port may form all of the exit conduit.

The exit conduit may be in the form of a tube. The inventors have found, however, that deposition of the aerosolised medicament can occur in a tubular exit conduit, which leads to uncertainty in the dose emitted by the inhaler. Nevertheless, a long exit conduit decreases the plume angle of the medicament aerosol as it exits the conduit and therefore reduces the deposition on the mouthpiece. However, this may increase deposition in the user's throat. Preferably, therefore, the length of the exit conduit (or port) is short, for example less than the diameter of the exit port of the aerosolising device. A short exit conduit (or port) increases the plume angle of the medicament aerosol as

it exits the conduit (or port) and therefore decreases the speed of the aerosol to reduce deposition in the user's throat. In a preferred arrangement, the length of the exit port is less than half the diameter of the exit port. The exit port may be an axial exit port.

Where the diameter of the exit port is not constant along its length, the length of the portion of the exit port having the smallest diameter should be less than that diameter.

In general, the exit port may be defined as a passage through a wall of the aerosolising device. In this case, the length of the exit port may depend on the thickness of the wall. The wall, or a portion thereof, may be tapered (or otherwise reduced in thickness) towards the exit port so that the length of the exit port is less than the maximum thickness of the wall. In particular, the perimeter of the exit port may be in the form of a knife-edge, i.e. a region of negligible thickness.

Where the aerosolising device comprises a vortex chamber, the wall in which the exit port is defined may be any wall of the vortex chamber. In a preferred arrangement, the exit port is defined in an upper wall of the vortex chamber. The upper wall may have an inner surface which defines the furthest extent of the vortex chamber from the inlet port in the axial direction. The inner surface may have any suitable form. For example, the inner surface may be conical, frustoconical, arcuate or hemispherical. In a preferred arrangement, however, the inner surface is planar. In particular, the inner surface may be substantially perpendicular to the axial direction. It has been found that such a configuration maximises the fine particle fraction of the emitted aerosol.

The inlet port to the aerosolising device may have any suitable cross-section. For example, the inlet port may have a substantially circular cross-section.

In a preferred configuration, the aerosolising device comprises a vortex chamber and the inlet port has an outer wall which defines the maximum extent of the inlet port in the radially outward direction of the vortex chamber. The extent of the outer wall in the axial direction of the vortex chamber is substantially equal to the maximum extent of the inlet port in the axial direction of the vortex chamber. The outer wall is substantially parallel with the wall of the vortex chamber.

In accordance with this feature, the inlet port is configured such that its radially outer wall is parallel to the wall of the vortex chamber along substantially the entire axial length of the inlet. In this way, a gas flow with entrained particles of medicament is able to enter the vortex chamber across the whole inlet port along a line which is parallel to the wall of the vortex chamber. This arrangement assists in maximising the proportion of the entrained particles which enter the boundary layer adjacent the wall of the vortex chamber where the shear forces generated by the vortex are at a maximum. In the boundary layer, the maximised shear forces produce maximum deagglomeration of the particles of medicament.

In a preferred arrangement, the outer wall of the inlet port is provided by the wall of the vortex chamber. In this way, the entrained particles of medicament are able to enter directly the boundary layer of the vortex across the whole inlet port.

The cross-section of the inlet port in accordance with this feature may take any suitable form relative to the outer wall. For example, the inlet port may be wedge-shaped or quadrant-shaped. In the preferred arrangement, for reasons of simplicity, the inlet port is rectangular in cross-section.

The inlet port may have a height in the axial direction up to the height of the vortex chamber. The

height of the inlet port may be greater than 1 mm and preferably less than 2 mm. In the preferred configuration, the height of the inlet port is 1.1 mm.

The width of the inlet port in the radial direction may be less than 1 mm. Preferably the width of the inlet port is greater than 0.2 mm, more preferably greater than 0.4 mm. The width of the inlet port is preferably less than 0.8 mm, more preferably less than 0.6 mm. In the preferred configuration, the width of the inlet port is 0.5 mm.

Advantageously, the maximum width of the inlet port is substantially equal to the width of the inlet port at the end furthest in the axial direction from the exit port of the vortex chamber. In this way, the particles of medicament entering the vortex chamber through the inlet port are encouraged initially towards the region of the chamber furthest from the exit port where the inlet port is widest. Thus, the residence time of the particles in the vortex chamber is maximised, thereby allowing more time for effective deagglomeration. The width of the inlet port may be constant along its axial extent.

The vortex chamber may comprise a bottom surface which defines the furthest extent of the vortex chamber from the exit port in the axial direction. In a preferred arrangement, the bottom surface also defines the furthest axial extent of the inlet port. According to this arrangement, the bottom wall of the inlet port is provided by the bottom surface of the vortex chamber. It has been found that such a configuration significantly reduces the deposition of medicament in the vortex chamber in use. The bottom surface need not be flat and, outside of the region of the inlet port, the vortex chamber may extend more or less in the axial direction than the furthest axial extent of the inlet port.

The inhaler may comprise an inlet conduit arranged

to supply a gas flow to the inlet port of the aerosolising device in use. The gas flow may contain particles of entrained medicament.

The inlet conduit may have a constant cross-sectional area in the tangential direction towards the aerosolising device. Preferably, however, the cross-sectional area of the inlet conduit decreases towards the aerosolising device. Thus, the inlet conduit may taper towards the aerosolising device. In this way, the velocity of a gas flow of constant mass flow rate increases as the flow moves towards the aerosolising device. The increasing velocity reduces the deposition of medicament entrained in the gas flow during its passage through the inlet conduit.

In embodiments of the invention, the rate of decrease of cross-sectional area with distance of the inlet conduit is between 1% and 30% per millimetre. The rate of decrease is preferably greater than 2% per mm, more preferably greater than 3% per mm and preferably less than 20% per mm, more preferably less than 10% per mm. In the preferred embodiment the rate of decrease is 5% per millimetre.

In a preferred configuration, the inlet conduit comprises an outer wall which is substantially tangential to the vortex chamber at the inlet port and an inner wall which converges towards the outer wall in the direction towards the vortex chamber. According to this arrangement, the inner wall guides the incoming gas flow towards the outer wall, such that the gas flow is directed towards the boundary layer of the vortex inside the vortex chamber.

The inlet conduit may be straight, for example the outer wall and the inner wall may be rectilinear. It is within the scope of the invention that only one of the outer wall and the inner wall is rectilinear. In an advantageous embodiment, the inlet conduit is arcuate. This has the advantage that angular momentum is imparted to the incoming gas flow and entrained medicament

particles as they pass through the inlet conduit even before they enter the vortex chamber. Thus, the inlet conduit is preferably concavely arcuate relative to the axis of the vortex chamber. The inlet conduit may be arcuate about the axis of the vortex chamber. In this way, the centrifugal force on the incoming gas flow propels the entrained particles of medicament towards the outside edge of the inlet conduit so that the particles enter the vortex chamber adjacent the boundary layer where shear forces are at a maximum.

The curvature of the inlet conduit is preferably sufficient that a tangent to the inner wall at the entrance of the conduit intercepts the outer wall before the end of the conduit. In this way, it is ensured that any particle following a straight path will reach the outer wall of the inlet conduit before entering the vortex chamber.

The arcuate inlet conduit may be any suitable length and have any suitable radius or radii of curvature. In one arrangement, the inlet conduit is in the form of a spiral around the aerosolising device. This arrangement allows a long inlet conduit, for example with only a slight taper, to be provided in a relatively compact way.

The inhaler may comprise a mouthpiece and the aerosolising device may be arranged to expel the medicament aerosol into the mouthpiece through an exit port. A mouthpiece locates the aerosolising device relative to the user's airway and allows the medicament aerosol to be directed into the airway. Preferably, the inhaler comprises at least one air passage which allows air to be inhaled through the mouthpiece in addition to the medicament aerosol. The provision of such an air passage allows the user to take a full breath even when the volume of the aerosol is relatively small. The additional air breathed in by a user may be beneficial in propelling the aerosol into the user's lungs.

In accordance with another embodiment of the present invention an inhaler is provided that includes a source of pressurized gas, a valve, the valve actuable between an open position and a closed position, and a drug entrainment device coupled to the source of pressurized gas. The drug entrainment device is disposed in a gas flow path between the source of pressurized gas and the valve.

In accordance with another embodiment of the present invention a method is provided for inhaling a powdered medicament. The method includes, prior to inhalation, pressurizing a drug entrainment device containing a powdered medicament via a source of compressed gas coupled to the drug entrainment device, opening a valve coupled to the drug entrainment device to entrain the powdered medicament a gas flow, and inhaling the powdered medicament.

BRIEF DESCRIPTION OF THE DRAWINGS

Some embodiments of the invention will now be described by way of example only and with reference to the accompanying drawings, in which:

Figure 1 is a schematic view, partially in section, of the general configuration of an inhaler;

Figure 2 is a sectional view along line A-A of a detail of the inhaler of Figure 1;

Figure 3 is a schematic view of an inhaler according to a general embodiment of the invention;

Figure 4a is a schematic view of an inhaler according to a first embodiment of the invention and Figure 4b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 4a over time;

Figure 5a is a schematic view of an inhaler according to a second embodiment of the invention and Figure 5b is a graph of the pressure in the drug entrainment chamber of the inhaler of Figure 5a over

time;

Figure 6 is a schematic view of a test rig for testing the operation of an inhaler in accordance with the invention;

Figure 7 is a plan view of the aerosolising device and valve of the test rig of Figure 6;

Figure 8 is a sectional view along line F-F of Figure 7;

Figures 9a and 9b are schematic sectional views illustrating the actuation of the valve in accordance with an embodiment of the invention;

Figures 10a and 10b are schematic sectional views of an alternative actuation mechanism for the valve of an embodiment of the invention;

Figures 11a and 11b are a partial sectional view and a plan view, respectively, of the breath actuation mechanism, valve and aerosolising device of an embodiment of the invention;

Figure 12a is a schematic view of an inhaler according to a third embodiment of the invention and Figure 12b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 12a over time;

Figure 13a is a schematic view of an inhaler according to a fourth embodiment of the invention and Figure 13b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 13a over time;

Figure 14a is a schematic view of an inhaler according to a fifth embodiment of the invention and Figure 14b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 14a over time;

Figure 15a is a schematic view of an inhaler according to a sixth embodiment of the invention and Figure 15b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 15a over

time;

Figure 16a is a schematic view of an inhaler according to a seventh embodiment of the invention and Figure 16b is a graph showing the pressure in the drug entrainment chamber of the inhaler of Figure 16a over time;

Figures 17a and 17b to 27a and 27b are schematic views, partially in section, illustrating the operation of valve arrangements for use with the invention;

Figure 28 is a sectional view, along line C-C of Figure 29, of a vortex chamber for use with the invention;

Figure 29 is a sectional view along line B-B of the vortex chamber of Figure 28;

Figure 30 is a graph of the variation in the fine particle fraction of the aerosol produced by the inhaler of Figure 1 with variation in the ratio of the diameter of the vortex chamber to that of the exit port;

Figure 31a is a side view of a vortex chamber with a round inlet port;

Figure 31b is a sectional view along line D-D of the vortex chamber of Figure 31a;

Figure 32a is a side view of a vortex chamber with a rectangular inlet port;

Figure 32b is a sectional view along line E-E of the vortex chamber of Figure 32a;

Figure 33 is a graph of the variation in the fine particle fraction of the aerosol produced by the vortex chambers of Figures 31 and 32;

Figures 34 to 37 show detail of embodiments of the exit port of an inhaler;

Figure 38 shows a vortex chamber with an arcuate inlet conduit; and

Figure 39a is a schematic view of an inhaler according to an eighth embodiment of the invention and Figure 39b is a graph of the pressure in the drug entrainment chamber of the embodiment of Figure 39a over

time.

In the various embodiments of the invention, components with corresponding function are given corresponding reference numerals.

DETAILED DESCRIPTION

Figure 1 shows schematically a prototype inhaler. The inhaler aerosolises a drug in dry powder form for inhalation by the user.

As shown in Figure 1, the inhaler comprises a vortex chamber (or nozzle) 1 having an exit port 2 and an inlet port 3 for generating an aerosol of medicament M. The vortex chamber 1 is located in a mouthpiece 4 through which the user inhales in use of the inhaler, as indicated by the arrow X. Air passages 5 are defined between the vortex chamber 1 and the mouthpiece 4 so that the user is able to inhale air in addition to the medicament aerosol M, as indicated by arrows Y.

The powdered medicament (or drug) M is provided to the vortex chamber 1 in an air flow from a drug entrainment device 6 via an inlet conduit 7. The drug entrainment device 6 is in the form of a cylindrical chamber with tangential inlet and outlet ports spaced in the axial direction. The drug may be supplied for transfer to the drug entrainment chamber in a foil blister or a standard gelatin capsule, containing 1 to 5 milligrams of powdered drug. The optimum particle size of the drug for delivery to the deep lung is 1 to 3 microns. If necessary an inert excipient, such as lactose, can be added to the drug to increase its bulk and improve its handling properties. Non-limiting examples of formulations with which the inhaler may be used are micronised pure drugs such as sodium cromoglycate, terbutaline sulphate and pure salbutamol sulphate, and spray-dried formulations of drugs such as insulin and paracetamol with a carrier such as hydroxy-ethyl starch.

The air flow to the drug entrainment device 6 is provided by a pump 8, represented in Figure 1 as a spring-powered piston pump. The pump 8 comprises a plunger 9 received in a pump cylinder 10 and biased into the pump cylinder 10 by a spring 11. The pump 8 is selected to have a capacity of less than 100 ml, preferably less than 50 ml and more preferably between 5 and 25 ml in order that the total size of the inhaler is relatively small. The pump 8 is capable of generating a pressure between 0.5 and 10 bar gauge, preferably less than 5 bar and more preferably less than 2 bar in order that the total size of the inhaler is relatively small. The flow rate through the inhaler is typically 1 to 5 litres per minute and may be adjusted for optimum performance with a particular medicament.

In use of the inhaler, the pump 8 is primed by retracting the plunger 9 against the force of the spring 11. The plunger 9 is retained in the primed position by a breath-actuated mechanism (not shown) until the user inhales. When the user inhales, the plunger 9 is released by the breath-actuated mechanism and the spring 11 forces the plunger 9 into the pump cylinder 10. In this way, air is forced through the drug entrainment device 6 where the powdered medicament M is entrained in the air flow. The air flow transports the medicament M to the vortex chamber 1, where a rotating vortex of medicament and air is created between the inlet port 3 and the outlet port 2. Rather than passing through the vortex chamber in a continuous manner, the powdered medicament entrained in the airflow enters the vortex chamber in a very short time (less than 0.3 seconds) and a proportion of the powdered medicament sticks to the walls of the vortex chamber. This powder is subsequently aerosolised by the high shear forces present in the boundary layer adjacent to the powder. The action of the vortex deagglomerates the particles of medicament M so that an aerosol M of powdered medicament exits the

vortex chamber 1 via the exit port 2. The aerosol is inhaled by the user through the mouthpiece 4.

The vortex chamber 1 can be considered to perform two functions: deagglomeration, the breaking up of clusters of particles into individual, respirable particles; and filtration, preferentially allowing particles below a certain size to escape more easily from the exit port 2. Deagglomeration breaks up cohesive clusters of powdered medicament into respirable particles, and filtration increases the residence time of the clusters in the vortex chamber 1 to allow more time for them to be deagglomerated. Deagglomeration can be achieved by creating high shear forces due to velocity gradients in the airflow in the vortex chamber 1. The velocity gradients are highest in the boundary layer close to the walls of the vortex chamber.

As shown in more detail in Figure 2, the vortex chamber 1 is in the form of a substantially cylindrical chamber. The vortex chamber 1 has a frustoconical portion in the region of the exit port 2. The inlet port 3 is substantially tangential to the perimeter of the vortex chamber 1 and the exit port 2 is generally concentric with the axis of the vortex chamber 1. Thus, gas enters the vortex chamber 1 tangentially via the inlet port 3 and exits axially via the exit port 2. Between the inlet port 3 and the exit port 2 a vortex is created in which shear forces are generated to deagglomerate the particles of medicament. The length of the exit port 2 is as short as possible to reduce the possibility of deposition of the drug on the walls of the exit port 2. In the embodiment shown, the vortex chamber 1 is machined from acrylic or brass, although a wide range of alternative materials is possible.

Figure 3 shows an inhaler according to an embodiment of the present invention comprising a low-pressure air source or reservoir in the form of a pump 8, a drug storage (or entrainment) chamber 6, an

aerosolising nozzle 1 in the form of a vortex chamber and a valve 18, preferably breath-actuated, at the exit 2 of the nozzle 1. In this embodiment, the drug entrainment chamber 6 is in the form of a disposable blister which contains a dose of powdered medicament.

In operation, the fluid system comprising the pump 8, drug storage chamber 6 and vortex chamber 1 is charged to a low-pressure (typically 1-2 bar gauge) by the pump 8. The user holds the mouthpiece 4 to their mouth and inhales, so that the breath-actuated valve 18 is triggered, releasing the pressurised air which aerosolises the drug and delivers it to the user.

This arrangement decouples the pressurisation of the air in the fluid system from the generation of the air flow to the vortex chamber 1 so that the inhaler aerosolises the drug using less energy than the inhaler shown in Figure 1. The inhaler can therefore be made smaller because a smaller volume of air is required.

An inhaler according to a first embodiment of the invention is shown in Figure 4a. In this embodiment, the fluid system is pressurised by a simple piston pump 8 to prime the inhaler. The valve 18 at the exit of the vortex chamber 1 is opened to aerosolise the drug and deliver it to the user. The pressure profile in the drug entrainment chamber 6 is shown in Figure 4b during priming, triggering of the valve 18 and delivery of the drug.

An inhaler according to a second embodiment of the invention is shown in Figure 5a. In this embodiment, the fluid system is pressurised by a piston pump 8. A spring 11 behind the plunger 9 of the pump 8 remains compressed during pressurisation of the fluid system. When the valve 18 is opened, for example triggered by the user inhaling, the spring 11 drives the plunger 9 into the pump cylinder 10, helping to maintain a more uniform pressure and flow through the drug entrainment chamber 6 and vortex chamber 1. The pressure profile in

the drug entrainment chamber 6 is shown schematically in Figure 5b in a corresponding manner to that in Figure 4b.

Figure 6 shows a test rig arrangement used to test the performance of an inhaler configuration according to the invention. The arrangement comprises an input 19 from a source of compressed air at 3 bar gauge connected to an air supply regulator 20. The air supply regulator 20 is connected to a reservoir 8 via an inlet valve 21 and is configured to charge the reservoir 8 to the required pressure (1.5 bar gauge). The volume of the reservoir 8 can be configured to be 5, 10, 30, 60 ml or another volume by connecting different lengths of tube to the reservoir assembly which forms the controlled volume of the reservoir. A pressure gauge 22 measures the pressure of air in the reservoir.

The regulator 20, inlet valve 21, reservoir 8 and pressure gauge 22 are all available from SMC Pneumatics of Indianapolis, Indiana, U.S.A.

The reservoir 8 is connected to a drug entrainment chamber 6, the internal volume of which is included in the controlled volume of the reservoir. The drug entrainment chamber 6 comprises two halves of a swirl chamber machined from aluminium, into which the dose of powdered drug can be loaded manually before assembling the two halves. A vortex chamber 1 (or nozzle) machined from brass is connected to the drug entrainment chamber 6 via a tube of internal diameter 1.2mm machined from Acetal.

The arrangement further comprises a valve assembly 18 comprising a resilient elastomer valve seal 23 on a cantilever arm 24 arranged to provide sealing force to seal the exit port 2 of the vortex chamber 1 when in the closed position. The cantilever arm 24 is shown in both the open and closed positions in Figures 6 and 8. The cantilever arm 24 pivots about a pivot 25 and is biased into the open position by a spring 26. A latch (not

shown) holds the valve arm 24 in the closed position and releases the arm when a further lever is moved. The configuration of the valve is shown in more detail in Figures 7 and 8.

The test rig is operated as follows. The dose of drug is loaded into the drug entrainment chamber 6 and the chamber is assembled. The valve arm 24 is moved to the closed position and latched there. The reservoir 8 is charged to the required pressure (1.5 barg) by opening the reservoir inlet valve 21 and then closing it once the reservoir 8 is charged. The regulator 20 sets the pressure.

To deliver the dose, the latch is released, allowing the valve arm 24 to move to the open position under the influence of the torsion spring 26 and the dose moves from the entrainment chamber 6 through the vortex chamber 1 and exits as an aerosol.

Figures 9a and 9b illustrate the operation of a latching arrangement for use with a valve 18 of the type described in relation to Figures 6 to 8. The valve arrangement in Figure 9 differs from that in Figures 6 to 8 in that the valve arm 24 is biased into the open position by a tension spring 26, rather than a torsion spring. As shown in Figure 9a, a latch member 27 is slidably received in a latch housing 28. The latch member 27 engages with a latch spigot 29 which extends perpendicularly from the valve arm 24 at the pivot 25 and is integral with the valve arm 24. The engagement of the latch member 27 and the latch spigot 29 prevents movement of the valve arm 24 about the pivot 25 under the bias of the tension spring 26.

As shown in Figure 9b, when the latch member 27 is withdrawn into the latch housing 28, the latch member 27 ceases to engage the latch spigot 29 and the valve arm 24 is free to rotate about the pivot 25 under the bias of the tension spring 26. The movement of the valve arm 24 removes the conical valve seal 23 from the exit port

2 of the vortex nozzle 1 so that an aerosol of powdered medicament is released from the vortex chamber 1.

Figures 10a and 10b illustrate an alternative configuration of the latching arrangement for the valve 18. According to this arrangement, a latch member 27 is L-shaped and engages with an upper end of the valve arm 24 to retain the valve arm in the closed position as shown in Figure 10a. Between the latch member 27 and the outer surface of the vortex chamber 1 is provided an expandable bladder 30 which is in fluid communication with the gas source (not shown) and the drug entrainment chamber 6 via a restriction 31. In operation of this arrangement, pressurised air is supplied simultaneously to the drug entrainment chamber 6 and the bladder 30. The increase in pressure causes the bladder 30 to expand and force the latch member 27 away from the valve arm 24 such that the valve arm 24 is freed to move about the pivot 25 under the influence of the spring 26. The bladder restriction 31 ensures that there is a slight delay in actuation of the valve latch to open the exit port 2 of the vortex chamber 1 so that the drug entrainment chamber 6 is fully pressurised before the valve opens.

Figures 11a and 11b show a variant of the latch mechanism which is operated by a breath actuation mechanism. According to this arrangement, the latch member 27 is in the form of a bell crank, one end of which engages an end of the valve arm 24 on the opposite side of the pivot 25 to the valve seal 23. The other end of the bell crank 27 engages a rubber (or elastomer) diaphragm 32. The diaphragm 32 includes holes 33 which are closed by sealing members 34 when the bell crank 27 is in the position shown in Figure 11a.

When the user inhales through the mouthpiece 4, the consequent reduction in pressure causes the diaphragm 32 to move towards the mouthpiece 4. This movement displaces the holes 33 from the sealing members 34 so

that the user is able to draw air through the holes 33 and the air passages 5. The movement of the diaphragm 32 also causes the bell crank to rotate about a pivot 35 so that the end of the bell crank 27 remote from the diaphragm 32 moves out of engagement with the end of the valve arm 24. The valve arm 24 is then free to move under the bias of a spring (not shown) to the open position shown in dashed lines in Figure 11a. In this way, fluid flow through the vortex chamber 1 is allowed by opening of the valve 18.

An inhaler according to a third embodiment of the invention is shown in Figure 12a. In this arrangement a restriction 36 is located between the pump 8 and the drug entrainment chamber 6. In use, the fluid system is pressurised by the pump 8. When the valve 18 at the exit 2 of the nozzle 1 is opened, for example triggered by the user inhaling, the instantaneous drop in pressure at the exit 2 leads to a sudden expansion of air in the drug entrainment chamber 6 and the nozzle 1, including air trapped between drug particles. This expansion helps initially to fluidise the drug. The restriction 36 controls the subsequent rate of flow from the pump 8 so that the delivery flow and pressure is more uniform, as shown in Figure 12b. In this way, the initial burst of high energy to fluidise the powder and the subsequent lower energy required for aerosolising the powder are achieved in a simple arrangement.

An inhaler according to a fourth embodiment of the invention is shown in Figure 13a. This embodiment has an additional valve 37 between the pump 8 and the drug entrainment chamber 6 as well as the valve 18 at the exit 2 of the nozzle 1. The valves 37, 18 work in a cascade fashion, with valve 18 being triggered (at point x in Figure 13b) shortly after valve 37 has opened. In use, the pump 8 is pressurised, and the additional valve 37 is opened by the user, for example triggered by the user inhaling. This allows the whole system to become

pressurised to approximately the pump pressure because the volume of the drug entrainment chamber 6 and the vortex chamber 1 is small in comparison with the pump volume. Opening the additional valve 37 triggers the opening of the exit valve 18 after a short delay sufficient to allow the pressure to equalise across the system. Once the exit valve 18 has opened, the inhaler functions similarly to the previously described embodiments. The advantage of this embodiment is that only the pump 8 is pressurised before the additional valve 37 is opened. The part of the system downstream of the valve is not pressurised until the inhaler is actuated and then for only a very short time. This means that the areas of the system containing powdered drug experience pressurisation for the minimum duration. This reduces the risk of powder loss in the event of a leak.

An inhaler according to a fifth embodiment of the invention is shown in Figure 14a. In this arrangement the valve 18 at the exit 2 of the nozzle 1 is triggered by the position of the plunger 9 or by the pressure in the system. The means of triggering may be, for example, mechanical, fluid or electronic. A suitable arrangement is shown in Figure 10. In use, the user pushes the plunger 9 and at a point where the pressure has reached a predetermined value, or the plunger 9 has reached a predetermined position, the valve 18 is opened and the aerosol delivered to the user.

An inhaler according to a sixth embodiment of the invention is shown in Figure 15a. This arrangement includes two pressurised reservoirs 8a and 8b, a larger reservoir 8a at a low pressure, 1-2 barg for example, and a smaller reservoir 8b at a higher pressure, 2-10 bar for example. The reservoirs may be two piston pumps of different diameters. A non-return valve 38 prevents air from the higher pressure reservoir 8b from flowing into the lower pressure reservoir 8a.

In use, both reservoirs 8a, 8b are pressurised. The

drug entrainment chamber 6 and the nozzle 1 are at the higher pressure because they are in fluid connection with the higher pressure reservoir 8b. When the user opens the valve 18 at the exit of the nozzle 1, preferably by inhaling, the instantaneous pressure drop inside the drug entrainment chamber 6 causes the drug to be fluidised as the air between the particles expands rapidly. Once the pressure in the drug entrainment chamber drops to below the pressure of the low-pressure reservoir 8a, air flows from the low-pressure reservoir 8a through the system, delivering the pre-fluidised drug to the user as an aerosol.

This arrangement is advantageous because a very small volume of higher pressure air can be used initially to fluidise the drug more effectively without adding significantly to the overall energy required for operation.

An inhaler according to a seventh embodiment of the invention is shown in Figure 16a. This embodiment includes the elements illustrated in Figure 15a and a control valve 39 between the smaller, higher-pressure reservoir 8b and its junction with the rest of the system. In use, both reservoirs 8a, 8b are pressurised. The drug entrainment chamber 6 and the nozzle 1 are at the lower pressure because they are in fluid connection with the lower-pressure reservoir 8a. The control valve 39 isolates the higher-pressure reservoir 8b. When the user opens the valve 18 at the exit 2 of the nozzle 1, preferably by inhaling, the instantaneous pressure drop inside the drug entrainment chamber 6 causes the drug to be fluidised as the air between the particles expands rapidly. Once the pressure in the low-pressure reservoir 8a drops to below a certain pre-determined level, the control valve 39 is opened, allowing the higher-pressure air to flow through the system and deliver any remaining drug to the user. The non-return valve 38 at the exit of the lower-pressure reservoir 8a prevents air flowing

from the higher-pressure reservoir 8b into the lower-pressure reservoir 8a. The control valve 39 may alternatively be actuated a set time after the start of the delivery pulse.

The operation of the control valve 39 may be achieved mechanically, for example by a pressure sensing diaphragm which moves a valve spool, or electronically for example by an electronic pressure sensor switching a solenoid valve, or by another means. A simple mechanical arrangement is preferable for reliability and low-cost.

This arrangement is advantageous because the higher-pressure air is reserved until towards the end of the delivery pulse when the bulk of the dose has already been delivered. The short pulse of higher-pressure air acts to clear any remaining drug from the system and thus increases the overall proportion of the dose that is delivered.

Figures 17a to 27a show various valve arrangements in the closed position and Figures 17b to 27b show the same valve arrangements in the open position.

Figures 17a and 17b illustrate a valve mechanism 18 for use with the invention. According to this arrangement, a pinch mechanism 40 restricts a flexible tube 41 to close the exit port 2 of the vortex chamber 1 of the inhaler.

Figures 18a and 18b show a further valve arrangement 18 for use with the invention. According to this arrangement the bottom surface 13 of the vortex chamber 1 is slidably received within the walls 12 of the vortex chamber 1. In the closed position, shown in Figure 18a, the base of the vortex chamber 13 is positioned such that the valve seal 23 closes off the exit port 2 of the vortex chamber 1. A pressure seal 42 is provided between the slidable base 13 and the walls 12 of the vortex chamber.

The valve arrangement shown in Figures 19a and 19b includes a sealed tip component 43 which is moulded with

the vortex chamber 1 and which is broken off to open the exit port 2 of the vortex chamber 1.

In Figures 20a and 20b, the exit port 2 of the vortex chamber 1 is sealed by a conical tip plug 44 which is biased into the open position shown in Figure 20b by a spring 26. The plug 44 is pushed into the closed position against the bias of the spring 26.

In Figures 21a and 21b, the base 13 of the vortex chamber 1 is flexible and is pushed against the exit port 2 of the vortex chamber 1 such that a valve seal 23 closes off the exit port 2 in the closed position shown in Figure 21a.

Figure 22a and Figure 22b shown an arrangement similar to that of Figures 9a and 9b. However, in this case the valve arm 24 carries a permanent magnet 45 and the exit of the vortex chamber 1 is provided with an electromagnetic coil 46. The electromagnetic coil 46 is powered to retain the valve arm 24 in position and the polarity of the coil is reversed to push the permanent magnet 45 away and open the outlet 2 of the vortex chamber 1.

Alternatively, a piece of ferromagnetic material such as soft iron can be used in place of the permanent magnet. In this case, the valve arm is biased to the open position by a spring.

Figures 23a and 23b show an arrangement similar to that of Figures 20a and 20b, but in this case the plug 44 has a flat tip provided with a valve seal 23. The plug 44 retracts in the open position, as shown in Figure 23b, so that it is flush with the base 13 of the vortex chamber 1.

In Figures 24a and 24b, a valve arrangement 18 utilising a flexible tube 41 and pinch mechanism 40 as described in relation to Figures 17a and 17b is provided between the drug entrainment chamber 6 and the vortex chamber 1.

In Figures 25a and 25b, the flexible tube 41 is

twisted to close the valve 18.

In Figures 26a and 26b, the drug entrainment chamber 6 in the form of a blister is held between triangular-section pressure seals. A cruciform piercing rod 47 punctures one membrane of the blister, so that the pressurised air supply can pressurise the drug M in the drug entrainment chamber 6 via a pressurised air passage way 48. As shown in Figure 26b, when the cruciform piercing rod 47 is driven through the remaining membrane of the blister the pressurised air is able to pass through the drug entrainment chamber 6 to entrain the powdered medicament. Thus, the membrane of the blister acts as a valve in this embodiment.

In Figures 27a and 27b, an inlet piercing rod 47 pierces the foil blister which forms the drug entrainment chamber 6 so that the drug entrainment chamber 6 can be pressurised with pressurised air via the pressurised air passageway 48. As shown in Figure 27b, an outlet piercing rod 49 pierces the membrane of the blister which forms the drug entrainment chamber 6 so that the air flow is able to entrain the powdered medicament for aerosolisation in the vortex chamber (not shown).

Figures 28 and 29 show the general form of the vortex chamber of the inhaler of Figures 1 to 27. The geometry of the vortex chamber is defined by the dimensions listed in Table 1. The preferred values of these dimension are also listed in Table 1. It should be noted that the preferred value of the height h of the conical part of the chamber is 0 mm, because it has been found that the vortex chamber functions most effectively when the top of the chamber is flat.

As shown in Figure 30, the fine particle fraction of the aerosol generated by the vortex chamber depends on the ratio of the diameters of the chamber D and the exit port D_e. The data represented in Figure 30 is shown in Table 2. The fine particle fraction is the

proportion of the particles of medicament emitted in the aerosol having an effective particle diameter of less than 6.8 microns. The normalised fine particle fraction is the emitted fine particle fraction divided by the fine particle fraction of the powdered medicament loaded into the inhaler. The medicament used was pure sodium cromoglycate.

Dimension		Value
D	Diameter of chamber	5.0 mm
H	Height of chamber	1.6 mm
h	Height of conical part of chamber	0.0 mm
D_e	Diameter of exit port	0.7 mm
t	Length of exit port	0.3 mm
a	Height of inlet port	1.1 mm
b	Width of inlet port	0.5 mm
α	Taper angle of inlet conduit	12°

Table 1 - Vortex chamber dimensions

Ratio D/D_e	Average fine particle fraction (<6.8um)	Normalised average fine particle fraction
2.0	64.7%	73.1%
3.1	70.8%	79.9%
4.0	75.5%	85.2%
6.0	81.0%	91.4%
7.1	83.5%	94.3%
8.0	83.2%	93.9%
8.6	80.6%	91.0%

Table 2 - Relationship between emitted fine particle fraction and ratio of vortex chamber diameter to exit port diameter.

It will be seen from Figure 30 that where the ratio of the diameters of the chamber and the exit port is 4 or more, the normalised fine particle fraction is over 85%. Thus, the deagglomeration efficiency of the vortex chamber is significantly improved where the ratio is in this range. With the preferred ratio of 7.1, a normalised fine particle fraction of 94.3% has been achieved.

Figures 31a and 31b show a vortex chamber 1 in which the inlet port 3 has a circular cross-section. As represented by the solid arrow in Figure 31b, a proportion of the airflow entering the vortex chamber via the inlet port 3 follows the wall 12 of the vortex chamber 1. The medicament entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the wall 12 of the vortex chamber 1, where the velocity gradient in the radial direction is at a maximum. The maximal velocity gradient results in maximal shear forces on the agglomerated particles of medicament and thus maximum deagglomeration.

However, as represented by the dashed arrow in Figure 31b, a proportion of the airflow entering the vortex chamber via the inlet port 3 does not follow the chamber wall 12, but rather crosses the chamber 1 and meets the wall 12 at a point opposite the inlet port 3. At this point, there is increased turbulence, because the flow must make an abrupt change of direction. This turbulence disturbs the boundary layer adjacent the wall 12 of the chamber 1 and thereby reduces the effectiveness of the deagglomeration of the medicament.

Figures 32a and 32b show a vortex chamber 1 in which the inlet port 3 has a rectangular cross-section. The rectangular cross-section maximises the length of the perimeter of the inlet port that is coincident with the wall 12 of the vortex chamber 1, such that the maximum air flow is introduced into the boundary layer

of the vortex. Similarly, the rectangular cross-section maximises the width of the perimeter of the inlet port 3 that is coincident with the bottom surface 13 of the vortex chamber 1. In this way, deposition of medicament in the vortex chamber 1 is prevented, because the vortex occupies the entire chamber 1.

In addition to having a rectangular cross-section, the inlet port 3 of Figures 32a and 32b is supplied by an inlet conduit 7 which tapers towards the vortex chamber 1. Thus, the inlet conduit 7 is defined by an inner wall 14 and an outer wall 15. The outer wall 15 is substantially tangential to the wall 12 of the vortex chamber 1. The spacing of the inner wall 14 from the outer wall 15 decreases towards the vortex chamber 1, so that the inner wall 14 urges the air flow into the vortex chamber 1 towards the boundary layer. Furthermore, the decreasing cross-sectional area of the inlet conduit 7 causes the flow velocity to increase, thereby reducing deposition of medicament on the way to the vortex chamber 1.

As indicated by the arrows in Figure 32b, all of the airflow entering the vortex chamber via the inlet port 3 follows the wall 12 of the vortex chamber 1. The medicament entrained in this airflow is therefore introduced directly into the airflow at the boundary layer adjacent the wall 12 of the vortex chamber 1, and deagglomeration is maximised.

Figure 33 shows that the average normalised fine particle fraction produced by the vortex chamber 1 of Figures 31a and 31b is only 49.7% compared to an average normalised fine particle fraction of 80.3% for the vortex chamber 1 of Figures 32a and 32b having an inlet port in the form of a slot of rectangular cross-section.

A further improvement can also be achieved if the upper surface 16 of the vortex chamber 1 is flat, as shown in Figures 34 to 36, rather than conical as shown in Figures 1, 28, 31 and 32. Thus, in this arrangement,

the upper surface 16 of the vortex chamber 1 is substantially perpendicular to the wall 12 of the chamber 1, and to the axis of the vortex. As shown in Figure 33, the average normalised fine particle fraction produced by the vortex chamber 1 with a flat upper surface (or top) is 87.8% compared to an average normalised fine particle fraction of 80.3% where the upper surface is conical.

Figures 34 to 37 show various options for the exit port 2 of the vortex chamber 1. The characteristics of the exit plume of the aerosol are determined, at least in part, by the configuration of the exit port 2. For example, if the aerosol leaves an exit port 2 of 1 mm diameter at a flow rate of 2 litres/minute, the velocity at the exit port 2 will be approximately 40 m/s. This velocity can be reduced to a typical inhalation velocity of 2 m/s within a few centimetres of the nozzle by providing a strongly divergent aerosol plume.

In Figure 34, the exit port 2 is a simple orifice defined through the upper wall 17 of the vortex chamber 1. However, the thickness of the upper wall 17 means that the exit port 2 has a length which is greater than its diameter. Thus, there is a risk of deposition in the exit port as the aerosol of medicament exits. Furthermore, the tubular exit port tends to reduce the divergence of the exit plume. These problems are solved in the arrangement of Figure 35 by tapering the upper wall 17 of the vortex chamber 1 towards the exit port 2 so that the exit port 2 is defined by a knife edge of negligible thickness. For an exit port 2 of diameter 1 mm, an exit port length of 2.3 mm gives a plume angle of 60°, whereas reducing this length to 0.3 mm increases the angle to 90°.

In Figure 36, the exit port 11 is annular and is also defined by a knife edge. This arrangement produces an exit plume that slows down more quickly than a circular jet, because the annular exit port has a

greater perimeter than a circular port of the same diameter and produces a jet that mixes more effectively with the surrounding static air. In Figure 37, multiple orifices form the exit port 2 and produce a number of smaller plumes which break up and slow down in a shorter distance than a single large plume.

Figure 38 shows an embodiment of the vortex chamber 1 in which the inlet conduit 7 is arcuate and tapers towards the vortex chamber 1. As shown by the arrows in Figure 38, the arcuate inlet conduit 7 urges the entrained particles of medicament M towards the outer wall 15 of the inlet conduit 7. In this way, when the medicament enters the vortex chamber 1 through the inlet port 3 the medicament is introduced directly into the boundary layer next to the wall 12 of the vortex chamber 1, where shear forces are at a maximum. In this way, improved deagglomeration is achieved.

The rapid sudden expansion when the valve 18 at the exit of the nozzle 1 is opened can cause a high velocity plume to exit the nozzle 1. This may not be advantageous because a high velocity plume is more likely to deposit powder on the user's throat and upper airways, which is undesirable. The applicants have found that the velocity of the plume increases with the size of the reservoir 8. Thus a larger reservoir 8 is likely to increase the drug deposited on the user's throat. However, if only a small reservoir is used, the volume of air contained therein may not be sufficient to aerosolise the entire dose. An eighth embodiment of an inhaler according to the invention, shown in Figure 39a, resolves these conflicting effects.

A variant of the embodiment of Figure 12 is shown in Figure 39a. In this arrangement, the restriction is located between two regions of the reservoir. The diameter of the orifice is such that it presents a greater restriction to the flow than the downstream elements of the system which are the drug storage

chamber, the nozzle, and the interconnecting passages. With this arrangement the volume of air in the initial burst can be larger than the volume of the drug entrainment chamber and nozzle. Figure 39b shows the pressure profile in the drug entrainment chamber 6 during priming, triggering and delivery of the drug.

This arrangement includes a partitioned reservoir 8 with a small orifice or restriction 36 fluidly connecting the two regions of the reservoir 8. The diameter of the orifice 36 is such that it presents a greater restriction to the flow than the downstream elements of the system, which are the drug entrainment chamber 6, the nozzle (or vortex chamber) 1, and the interconnecting passages.

In use, the reservoir 8 is charged to a given pressure, for example 1.5 bar. Both regions are at this pressure. When the user opens the valve 18 at the exit of the nozzle 1, preferably by inhaling, the air in the downstream region, closest to the nozzle 1, undergoes a sudden expansion and is discharged rapidly to the drug entrainment chamber 6 causing the drug to be fluidised in the manner described in previous embodiments. The air in the region upstream from the partition is prevented from discharging as quickly as the air in the downstream region because the restriction 36 limits the flow between the two regions of the reservoir 8. This air discharges more slowly after the initial sudden expansion of the air in the downstream region. Thus, instantaneously, the reservoir 8 presents only the downstream volume to the drug entrainment chamber 6. Subsequently the full volume of the reservoir 8 flows through the drug entrainment chamber 6 and the nozzle 1.

This arrangement is advantageous because only a portion of the air in the reservoir 8 provides the initial sudden expansion, but a larger volume of air is available to aerosolise the dose of medicament. In this way, a low exit plume velocity can be maintained without

reducing the overall reservoir size.

Tables 3 and 4 show the analysis of the aerosol produced by an inhaler described herein using an Astra Draco Multi-Stage (4/5) Liquid Impinger (MLI). The performance of the inhaler was tested using three medicament formulations: micronised sodium cromoglycate, terbutaline sulphate and micronised salbutamol sulphate. In each case, the dose of drug was 1 milligram and the flow rate of air through the vortex chamber was 3 litres/minute.

Medicament	Medicament FPF	Delivered FPF	Deagglomeration efficiency
Micronised Sodium Cromoglycate	88.6%	83.6%	94%
Terbutaline Sulphate	85.8%	70.2%	83%
Micronised Salbutamol Sulphate	88.7%	73.7%	83%

Table 3 - Fine particle fractions (FPF) for topical delivery of medicament (<6.8 microns)

Initially, the fine particle fraction of the powdered medicament before aerosolisation was determined, as this represents the maximum achievable fine particle fraction for the aerosol. To determine the initial fine particle fraction, the powdered medicament was fully dispersed in a non-solvent, cyclohexane, by means of ultrasonic agitation and the particle distribution measured using a laser particle sizer available from Malvern Instruments Limited of Malvern UK. For topical delivery of the medicament (Table 3) the fine particle fraction is defined as the proportion of particles with a particle size of less

than 6.8 microns. For systemic delivery of the medicament (Table 4) the fine particle fraction is defined as the proportion of particles with a particle size of less than 3 microns. The fine particle fraction of the aerosol was determined and compared to the corresponding fine particle fraction before aerosolisation to give a value for deagglomeration efficiency as a percentage of the maximum achievable fine particle fraction.

Medicament	Medicament FPF	Delivered FPF	Deagglomeration efficiency
Micronised Sodium Cromoglycate	66.7%	62.2%	93%
Terbutaline Sulphate	54.6%	44.6%	82%
Micronised Salbutamol Sulphate	57.6%	52.6%	91%

Table 4 - Fine particle fractions (FPF) for systemic delivery of medicament (<3 microns)

The results in Table 3 and 4 show that for each of the three medicaments the deagglomeration efficiency is over 80% for both topical and systemic delivery and in many cases is over 90%.

The inhaler in accordance with embodiments of the invention is able to generate a relatively slow moving aerosol with a high fine particle fraction. The inhaler is capable of providing complete and repeatable aerosolisation of a measured dose of powdered drug and of delivering the aerosolised dose into the patient's inspiratory flow at a velocity less than or equal to the velocity of the inspiratory flow, thereby reducing deposition by impaction in the patient's mouth.

Furthermore, the efficient aerosolising system allows for a simple, small and low cost device, because the energy used to create the aerosol is small. The fluid energy required to create the aerosol can be defined as the integral over time of the pressure multiplied by the flow rate. This is typically less than 5 joules and can be as low as 3 joules.

Although the aerosol of medicament has been described herein as an aerosol of powdered medicament in air, the medicament may be dispersed in any other gas or mixture of gases, as required. Furthermore, although the invention has been described in terms of apparatus, the invention also extends to a method of generating an inhalable aerosol of a powdered medicament as described herein.

In summary, an inhaler for producing an inhalable aerosol of a powdered medicament includes a pump in fluid communication with a drug entrainment device and an aerosolising device. A valve is provided at the exit of the aerosolising device so that the whole fluid system can be pressurised before the valve is opened to allow air flow to entrain and aerosolise the powdered medicament. The inhaler allows efficient aerosolisation of a powdered medicament using a smaller volume of air.

The aerosolising device is in the form of a cylindrical vortex chamber. The vortex chamber has a tangential inlet port and an axial exit port. The ratio of the diameter of the vortex chamber to the diameter of the exit port is between 4 and 12. The length of the exit port is less than its diameter. The cross-section of the inlet port is rectangular and is defined at the bottom and at the radially outermost edge by the walls of the vortex chamber. The cross-sectional area of the inlet conduit, which supplies the medicament in a gas flow to the inlet port, decreases in the direction towards the vortex chamber. The inlet conduit can be curved. The inhaler is capable of repeatably producing

an aerosol of a medicament with a high proportion of particles in the range 1 to 3 microns, while using a relatively small amount of energy.

In the preceding specification, the invention has been described with reference to specific exemplary embodiments thereof. It will, however, be evident that various modifications and changes may be made thereto without departing from the broader spirit and scope of the invention as set forth in the claims that follow. The specification and drawings are accordingly to be regarded in an illustrative manner rather than a restrictive sense.

CLAIMS

1. An inhaler for producing an inhalable aerosol of a powdered medicament, the inhaler comprising:

a drug entrainment device for entraining a powdered medicament in a gas flow;

a gas source arranged to supply pressurised gas to the drug entrainment device; and

a valve which is selectively actuable to prevent gas flow through the drug entrainment device,

wherein the drug entrainment device is located in a flow path between the gas source and the valve.

2. An inhaler as claimed in claim 1 further comprising an aerosolising device.

3. An inhaler as claimed in claim 2, wherein the aerosolising device comprises the drug entrainment device.

4. An inhaler as claimed in claim 2, wherein the aerosolising device is located in a flow path between the drug entrainment device and the valve.

5. An inhaler as claimed in claim 2, wherein the valve is located in a flow path between the drug entrainment device and the aerosolising device.

6. An inhaler as claimed in any of claims 2 to 5, wherein the aerosolising device is in the form of a vortex chamber of substantially circular cross-section having a substantially tangential inlet port and a substantially axial exit port.

7. An inhaler as claimed in any preceding claim, wherein the valve is actuated in response to a level of pressure generated by the gas source.

8. An inhaler as claimed in claim 7, wherein the valve is actuated by pressure generated by the gas source.

9. An inhaler as claimed in any preceding claim comprising a further valve located in a flow path between the gas source and the drug entrainment device.

10. An inhaler as claimed in any preceding claim, wherein the valve(s) comprise(s) a membrane which is arranged to be punctured to open the valve.

11. An inhaler as claimed in any preceding claim comprising a first gas source arranged to supply pressurised gas to the drug entrainment device at a first pressure and a second gas source arranged to supply pressurised gas to the drug entrainment device at a second pressure, wherein the second pressure is greater than the first pressure.

12. An inhaler comprising:

a source of pressurized gas;

a valve, the valve actuable between an open position and a closed position; and

a drug entrainment device coupled to the source of pressurized gas, the drug entrainment device disposed in a gas flow path between the source of pressurized gas and the valve.

13. The inhaler as recited in claim 12 further comprising an aerosolising device coupled to the drug entrainment device.

14. The inhaler as recited in claim 12 wherein the drug entrainment device comprises an aerosolising device.

15. The inhaler as recited in claim 13 wherein the aerosolising device is disposed in a gas flow path

between the drug entrainment device and the valve.

16. The inhaler as recited in claim 13, wherein the valve is located in a gas flow path between the drug entrainment device and the aerosolising device.

17. The inhaler as recited in claim 13, wherein the aerosolising device defines a vortex chamber having a substantially circular cross-section, a tangential inlet port and an axial exit port.

18. The inhaler as recited in claim 12, wherein the valve is actuable in response to a level of pressure generated by the gas source.

19. The inhaler as recited in claim 18, wherein the valve is actuable by the pressure generated by the gas source.

20. The inhaler as recited in claim 18, further comprising a sensor coupled to the valve, wherein the level of pressure is detected by the sensor.

21. The inhaler as recited in claim 20, wherein the sensor is an electronic pressure sensor.

22. The inhaler as recited in claim 12 further comprising a second valve disposed in a gas flow path between the gas source and the drug entrainment device.

23. The inhaler as recited in claim 12 wherein the valve comprises a rupturable membrane.

24. The inhaler as recited in claim 12 wherein the gas source is arranged to supply pressurised gas to the drug entrainment device at a first predetermined pressure and further comprising a second gas source arranged to

supply a second pressurised gas to the drug entrainment device at a second predetermined pressure, wherein the second predetermined pressure is greater than the first pressure.

25. The inhaler as recited in claim 12, further comprising a mouthpiece coupled to the drug entrainment device.

26. The inhaler as recited in claim 13, further comprising a mouthpiece coupled to the aerosolising device.

27. The inhaler as recited in claim 12, wherein the drug entrainment device is a blister containing the powdered medicament.

28. The inhaler of claim 12, wherein the valve comprises a resilient elastomer valve seal on a cantilever arm.

29. The inhaler of claim 12, wherein the valve is breath actuated.

30. A method for inhaling a powdered medicament, comprising

prior to inhalation, pressurizing a drug entrainment device via a source of compressed gas coupled to the drug entrainment device, the drug entrainment device containing a powdered medicament;

opening a valve coupled to the drug entrainment device to entrain the powdered medicament a gas flow; and

inhaling the powdered medicament.

31. The method of claim 30, wherein the valve is breath actuated, and the step of opening comprises inhaling.

32. The method of claim 30, wherein an aerosolising device is coupled to the drug entrainment device, and after the opening step, the powdered medicament in the gas flow is aerosolized in the aerosolising device prior to being inhaled.

33. The method as recited in claim 30 wherein the opening step is performed in response to a level of pressure generated by the gas source.

34. The method as recited in claim 33, wherein the level is detected by a sensor.

35. The method as recited in claim 30, wherein the step of opening the valve comprises rupturing a membrane.

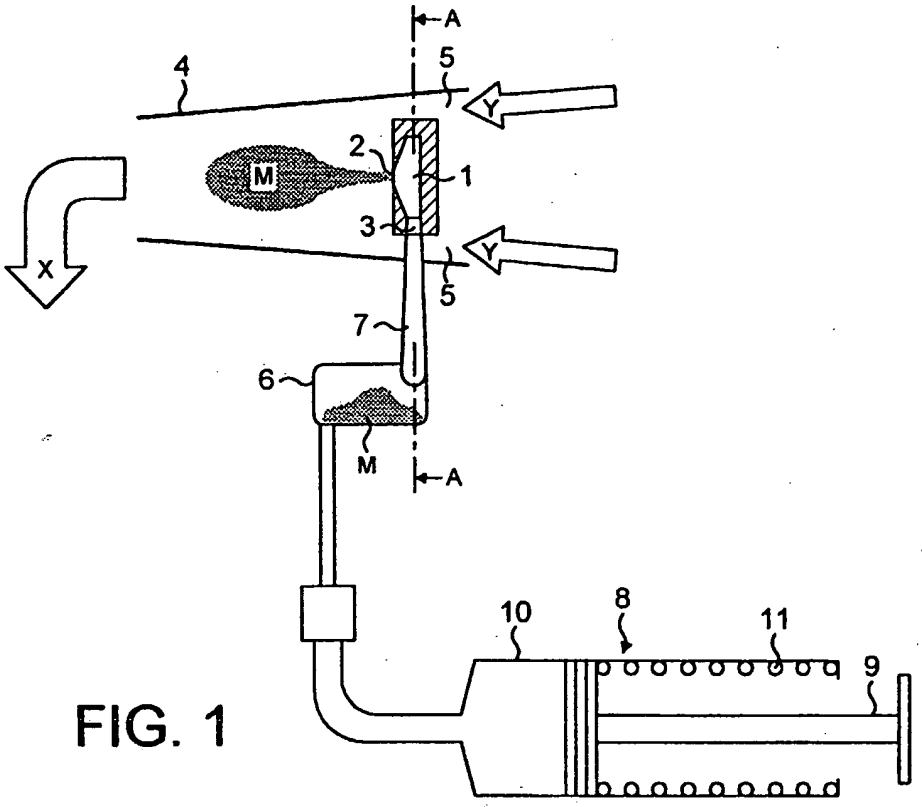

FIG. 1

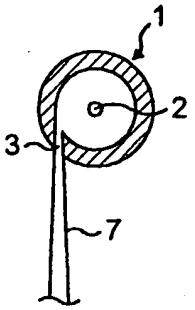

FIG. 2

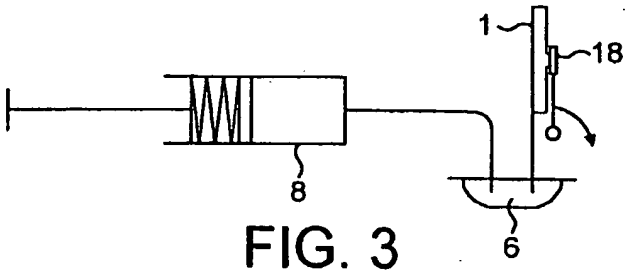

FIG. 3

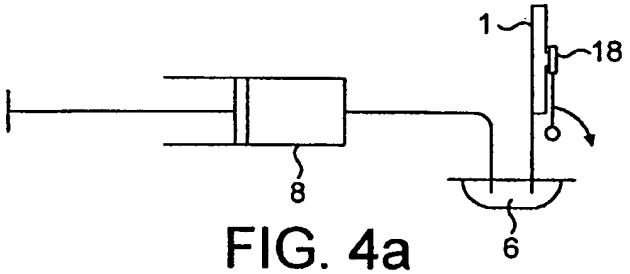

FIG. 4a

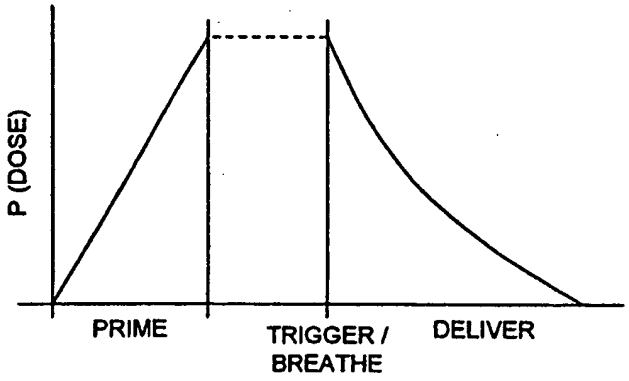

FIG. 4b

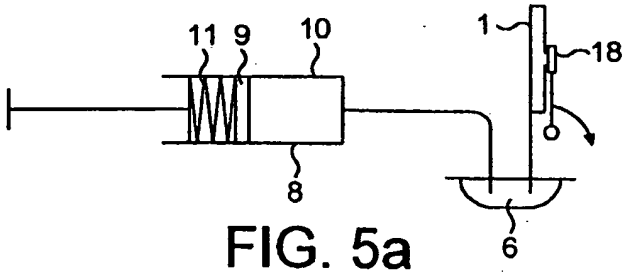

FIG. 5a

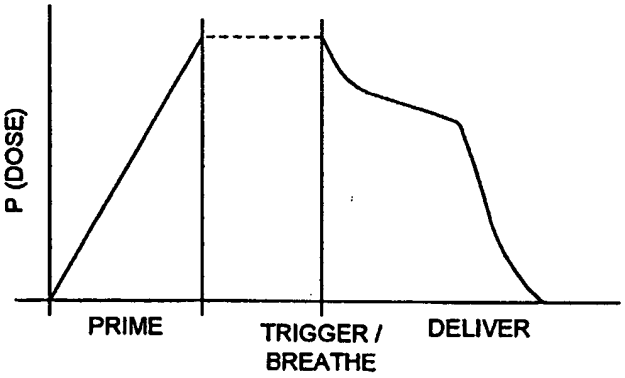

FIG. 5b

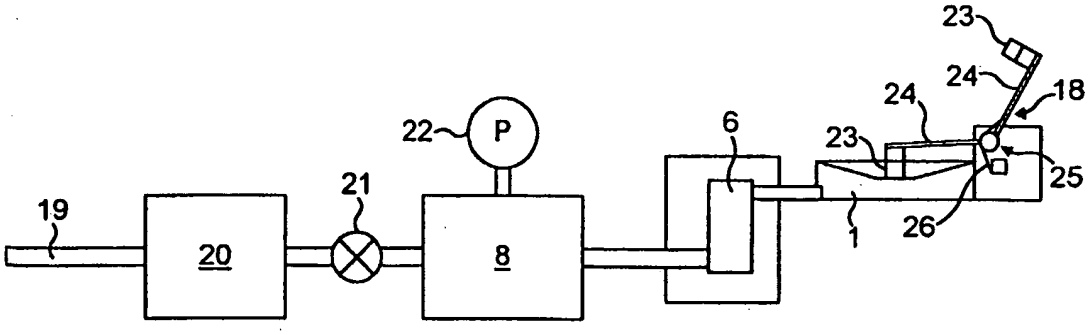

FIG. 6

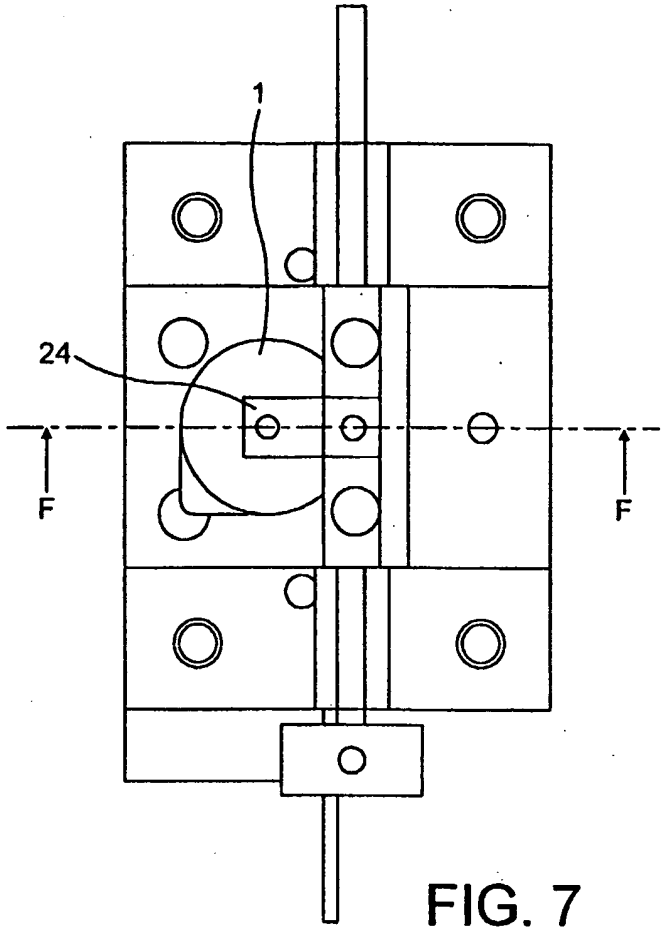

FIG. 7

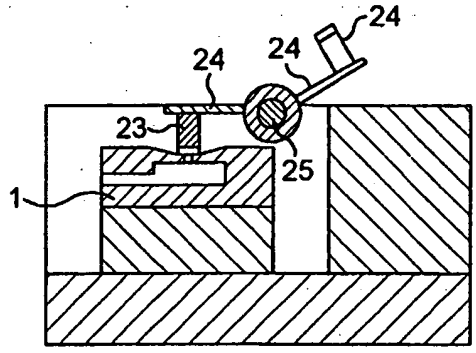

FIG. 8

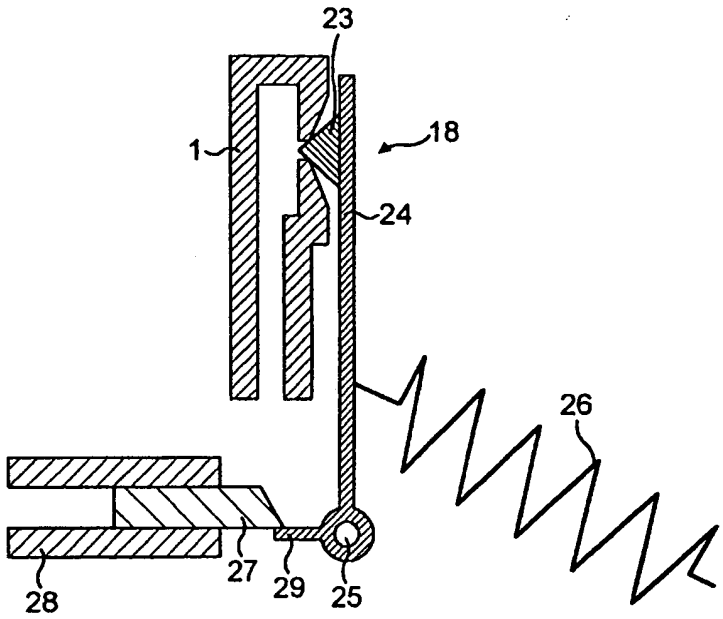

FIG. 9a

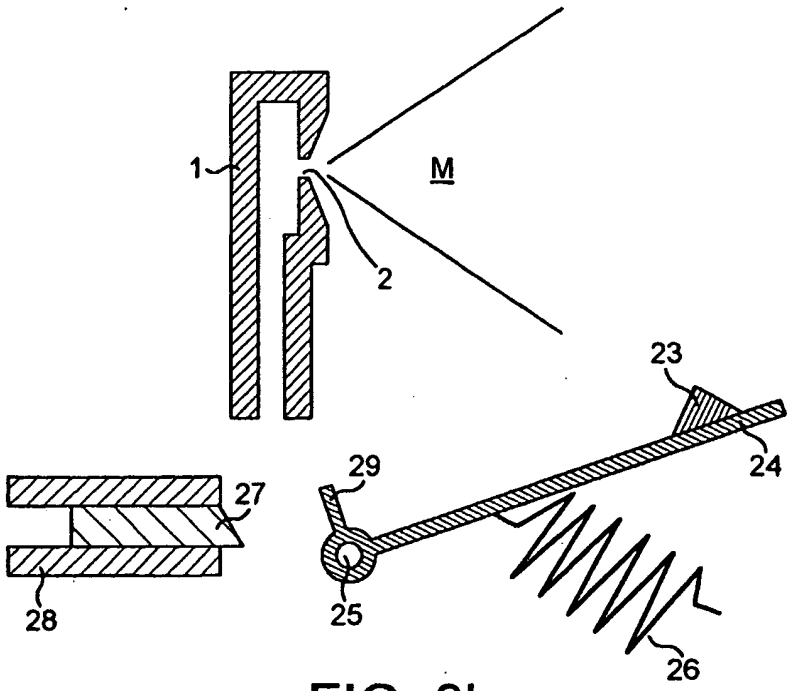

FIG. 9b

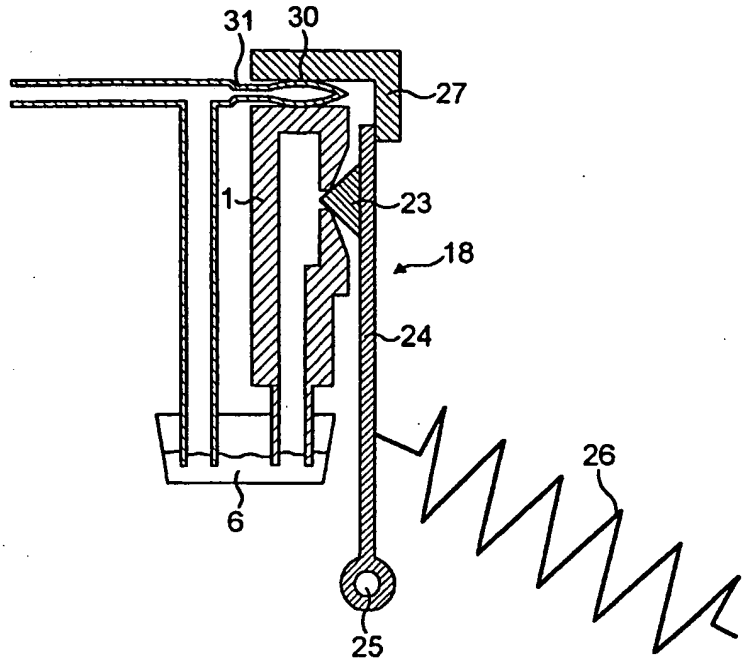

FIG. 10a

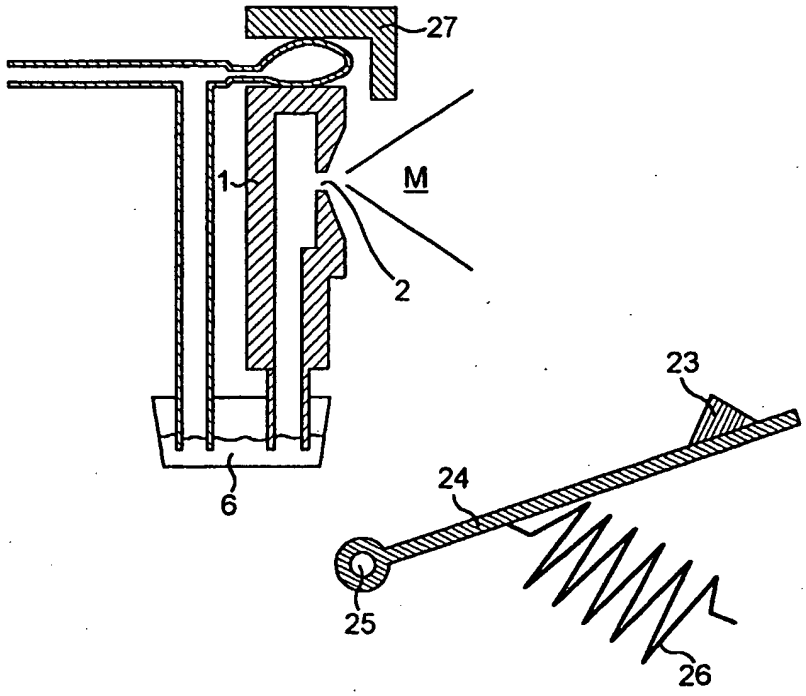

FIG. 10b

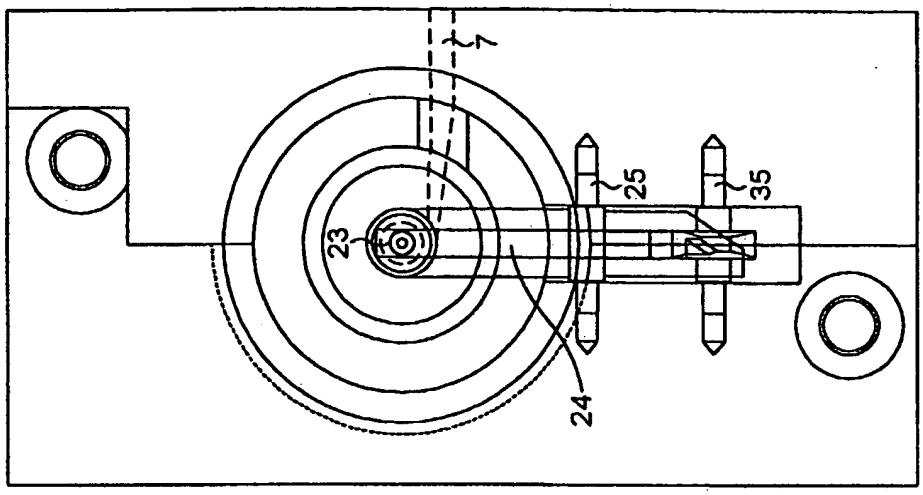

FIG. 11b

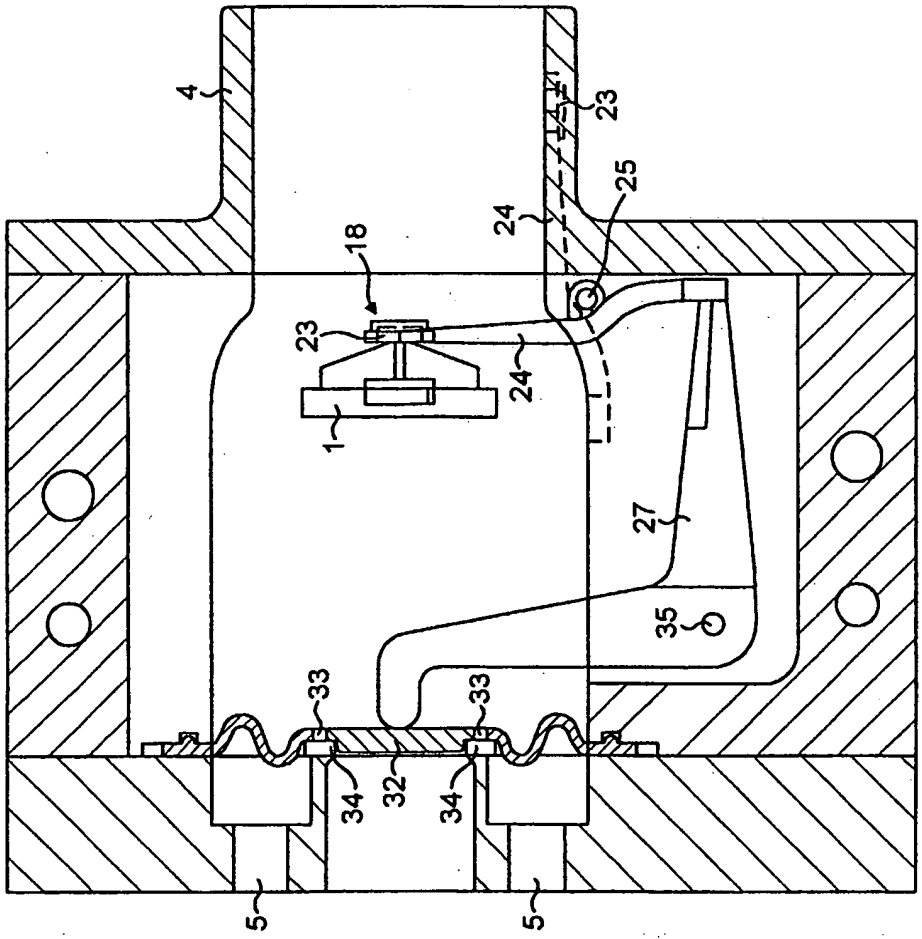

FIG. 11a

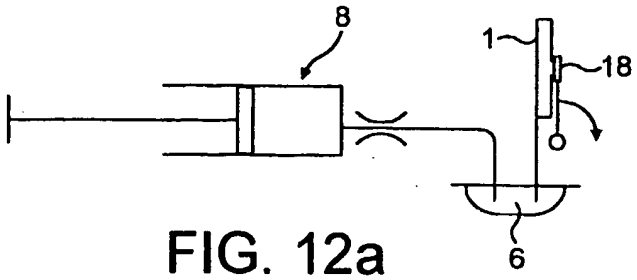

FIG. 12a

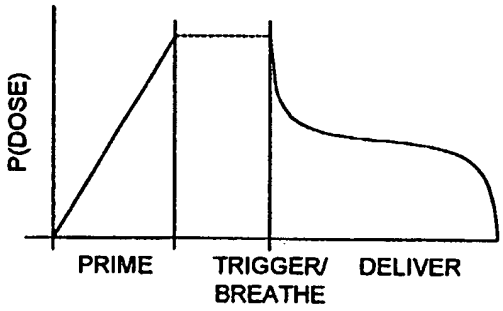

FIG. 12b

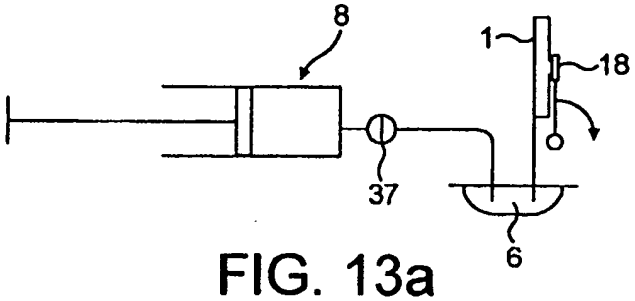

FIG. 13a

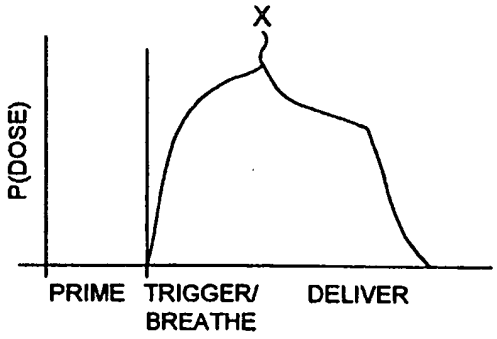

FIG. 13b

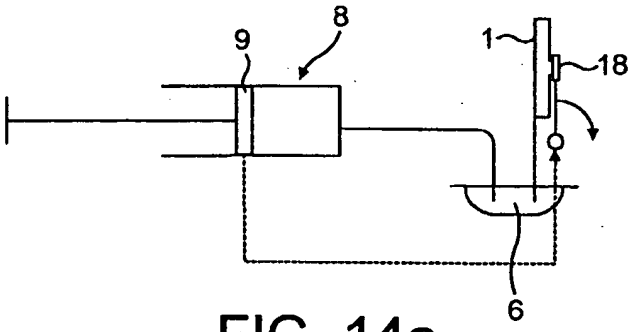

FIG. 14a

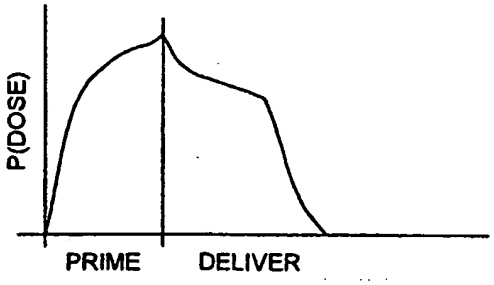

FIG. 14b

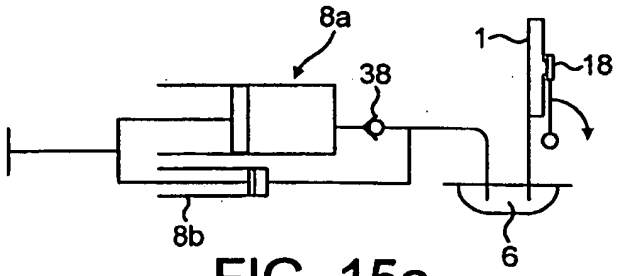

FIG. 15a

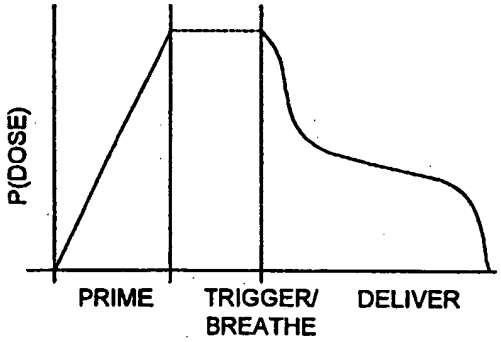

FIG. 15b

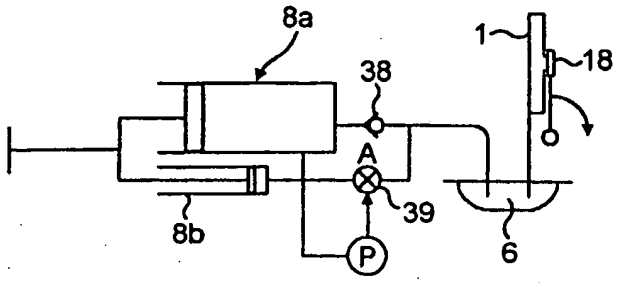

FIG. 16a

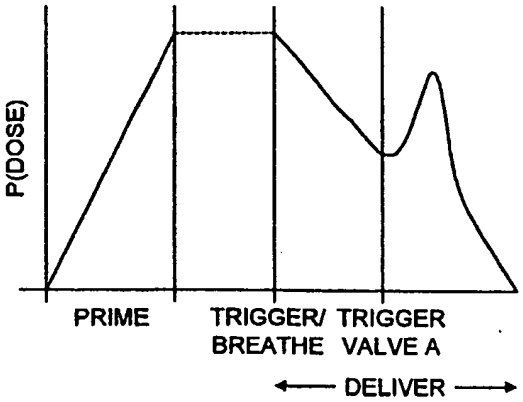

FIG. 16b

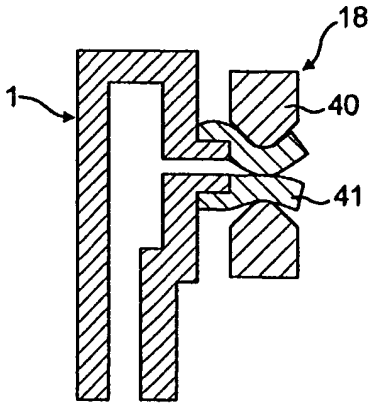

FIG. 17a

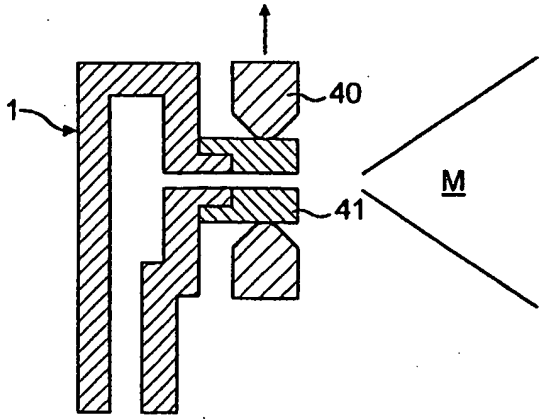

FIG. 17b

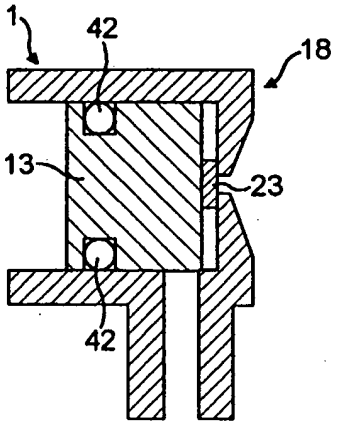

FIG. 18a

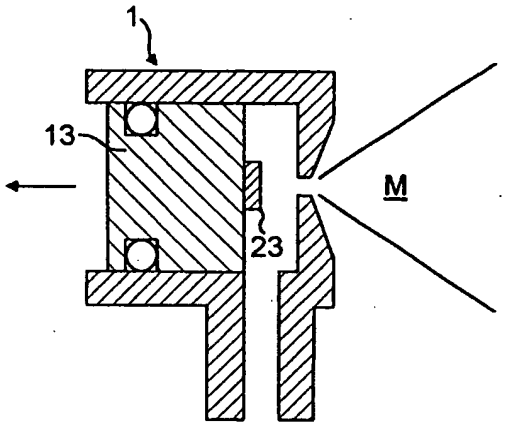

FIG. 18b

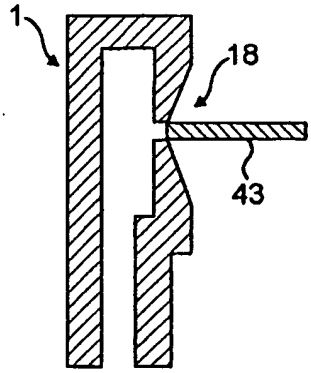

FIG. 19a

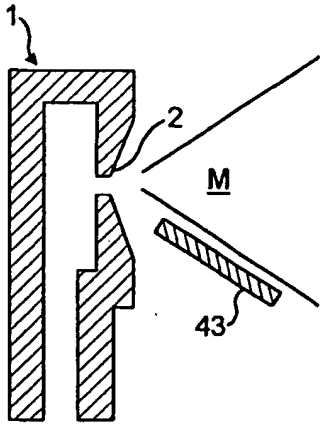

FIG. 19b

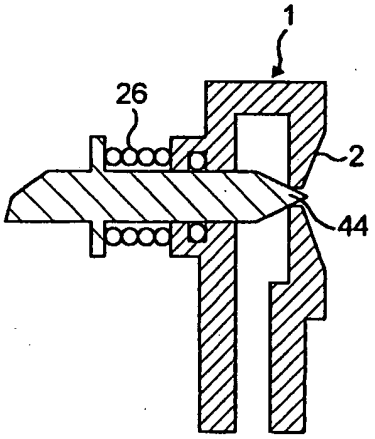

FIG. 20a

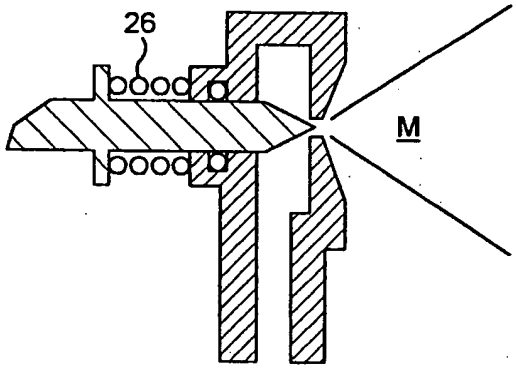

FIG. 20b

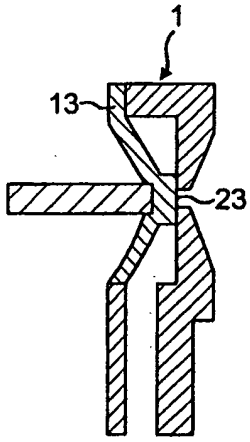

FIG. 21a

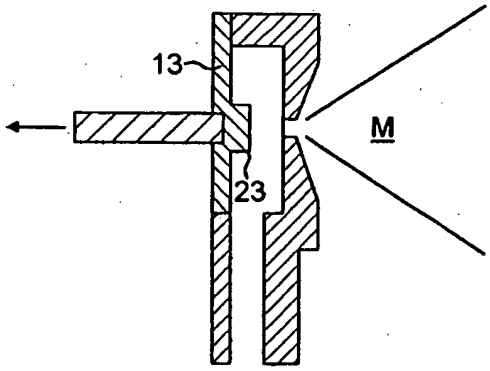

FIG. 21b

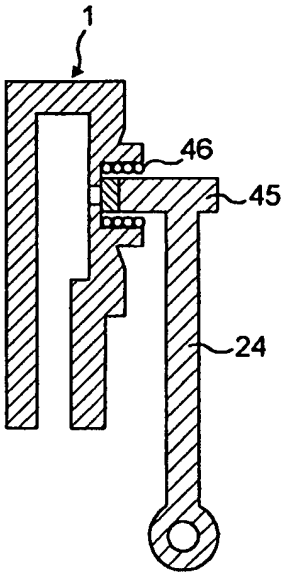

FIG. 22a

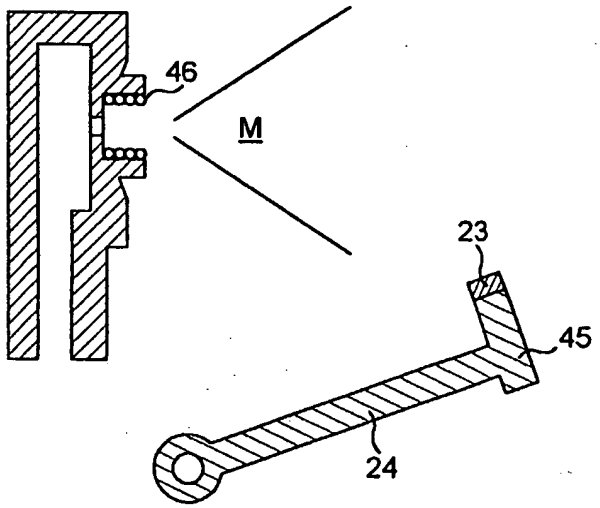

FIG. 22b

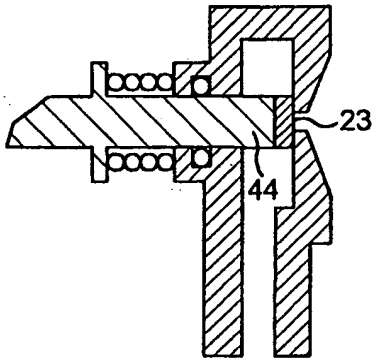

FIG. 23a

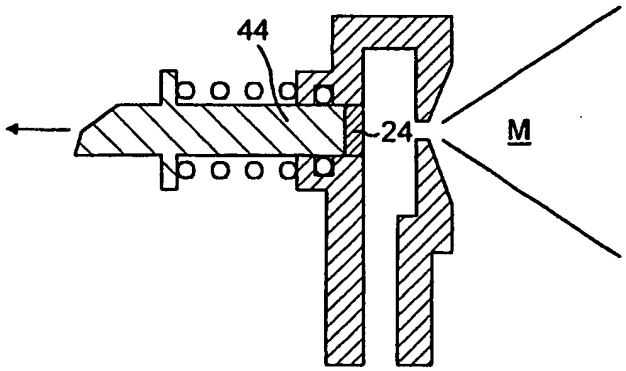

FIG. 23b

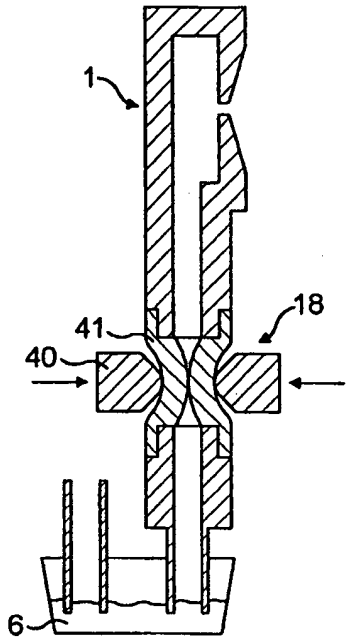

FIG. 24a

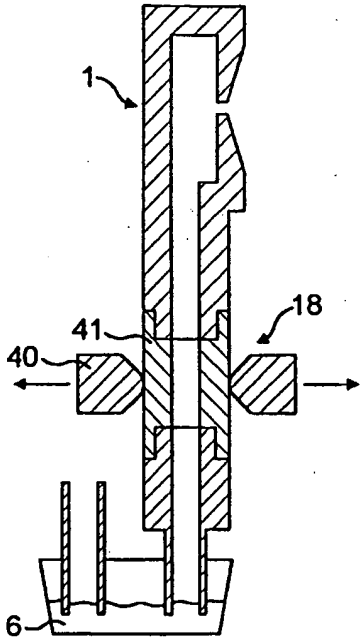

FIG. 24b

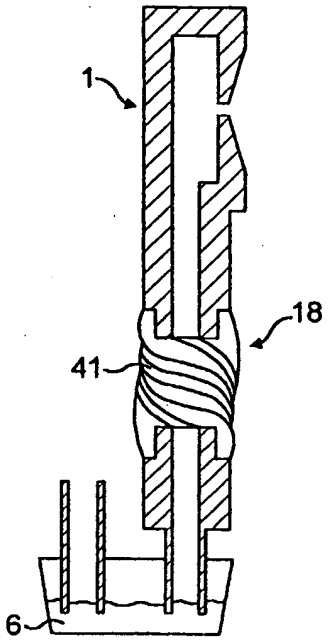

FIG. 25a

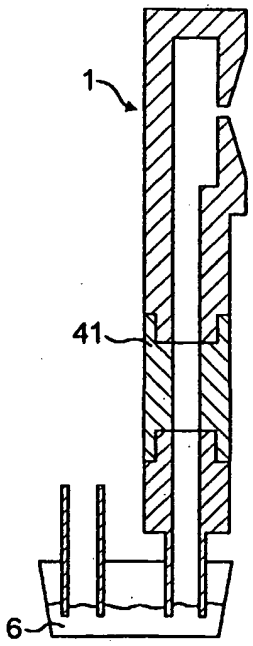

FIG. 25b

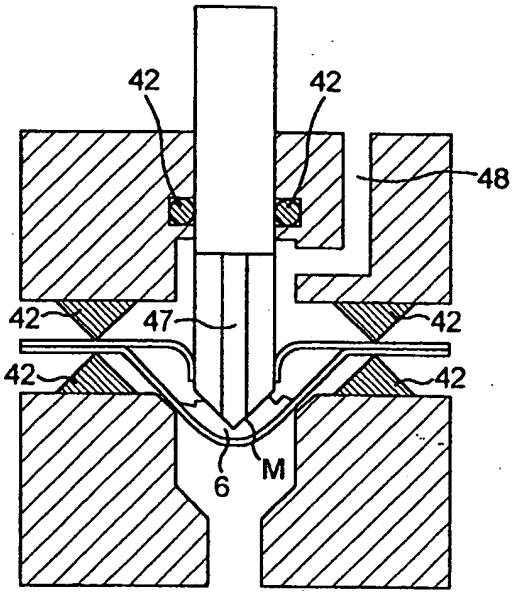

FIG. 26a

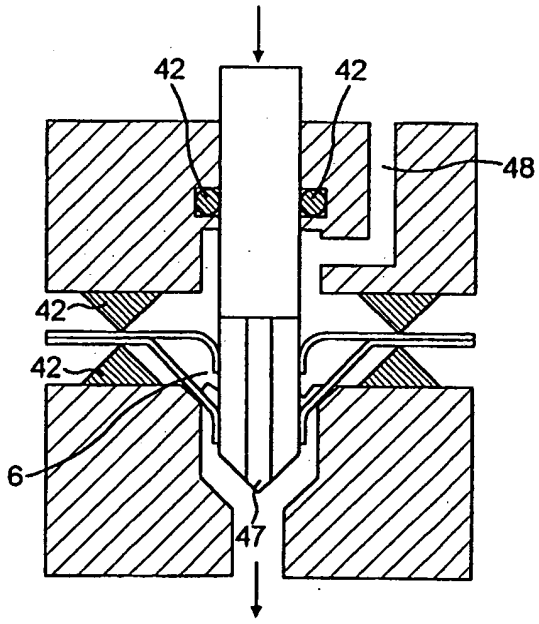

FIG. 26b

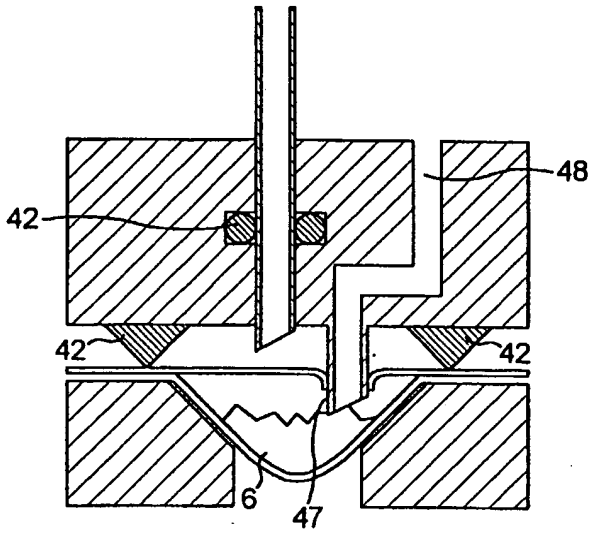

FIG. 27a

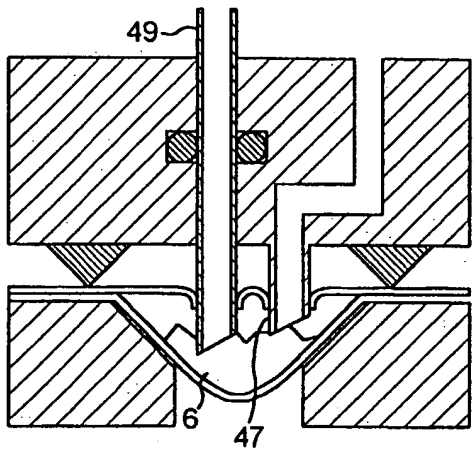

FIG. 27b

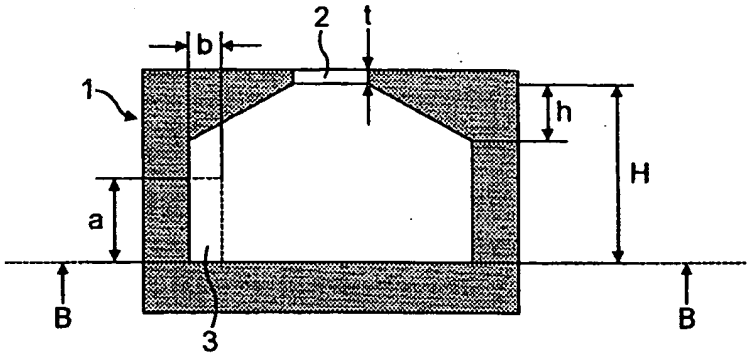

FIG. 28

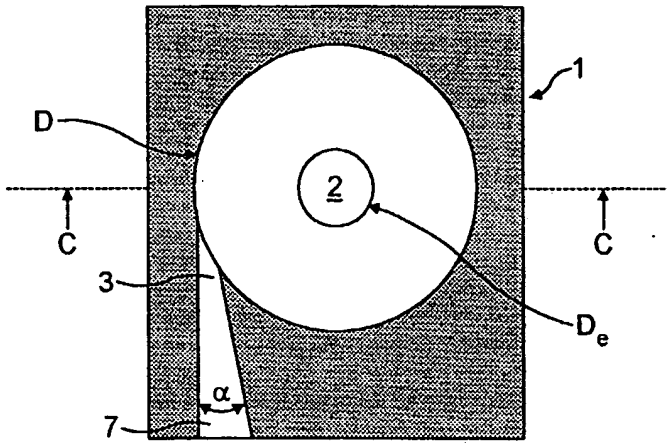

FIG. 29

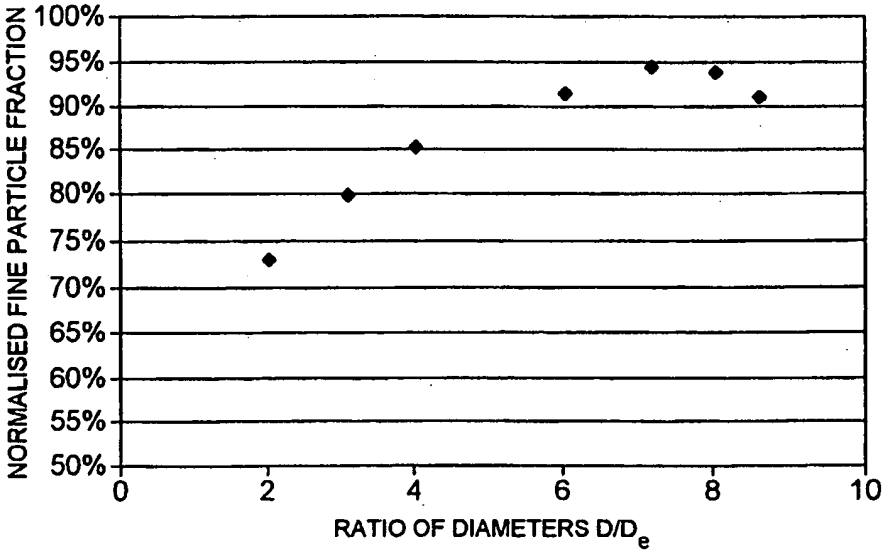

FIG. 30

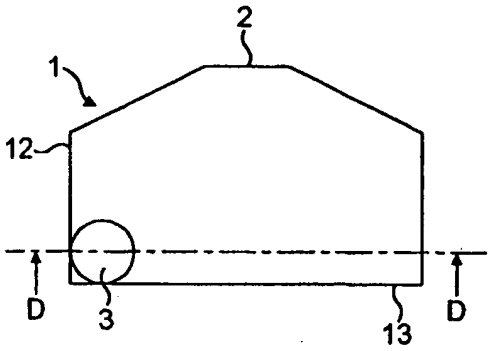

FIG. 31a

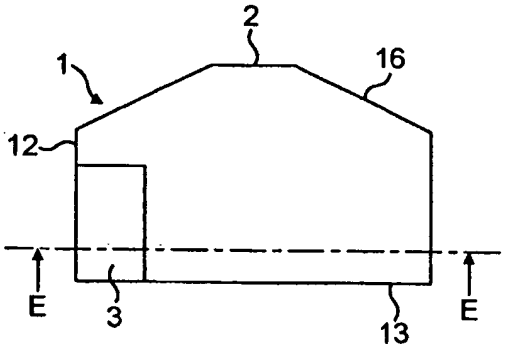

FIG. 32a

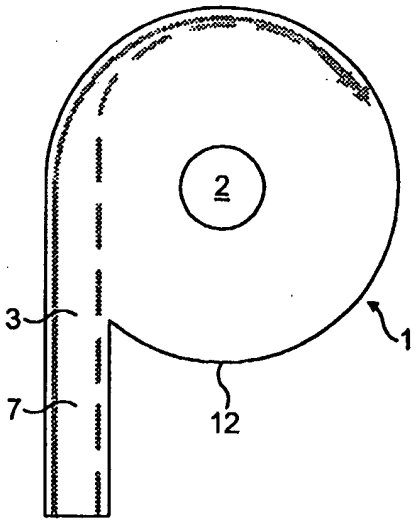

FIG. 31b

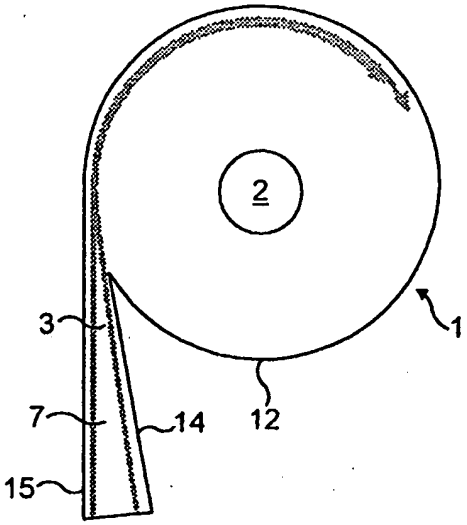

FIG. 32b

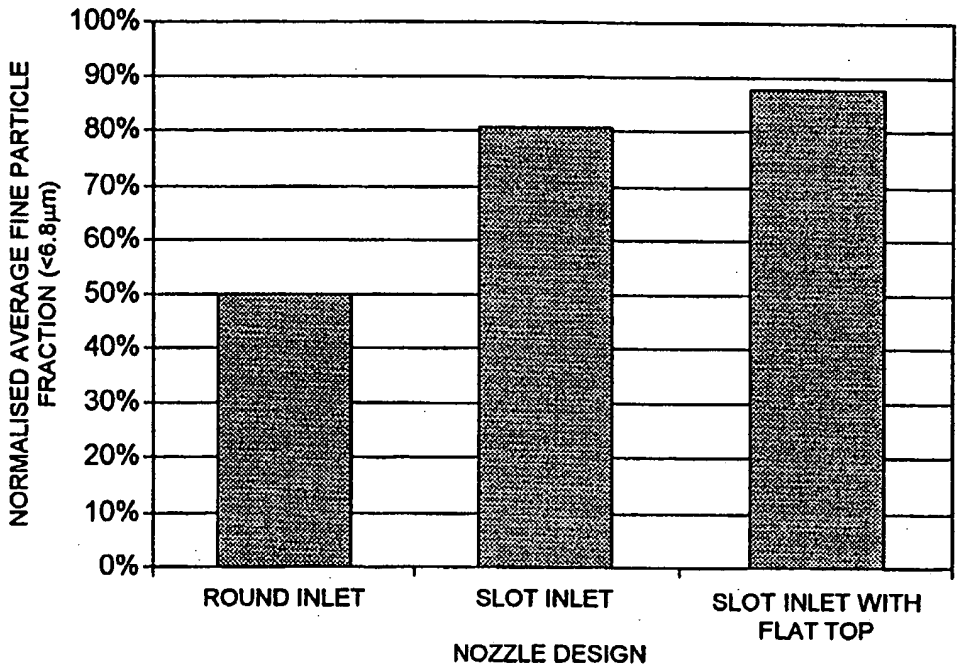
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
NORMALISED AVERAGE FINE PARTICLE FRACTION (<6.8µm)
ROUND INLET
SLOT INLET
SLOT INLET WITH FLAT TOP
NOZZLE DESIGN

FIG. 33

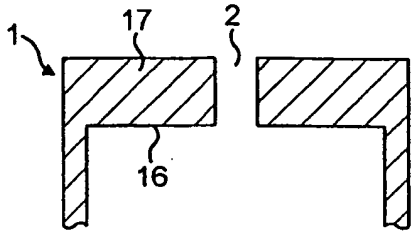

FIG. 34

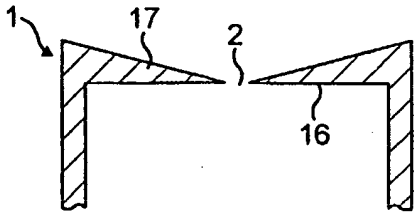

FIG. 35

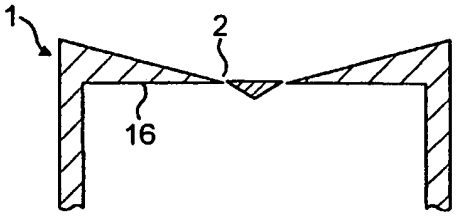

FIG. 36

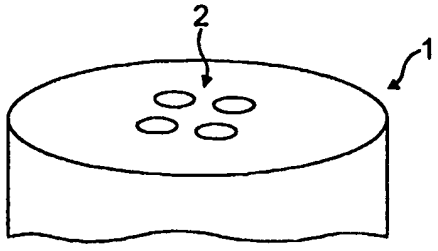

FIG. 37

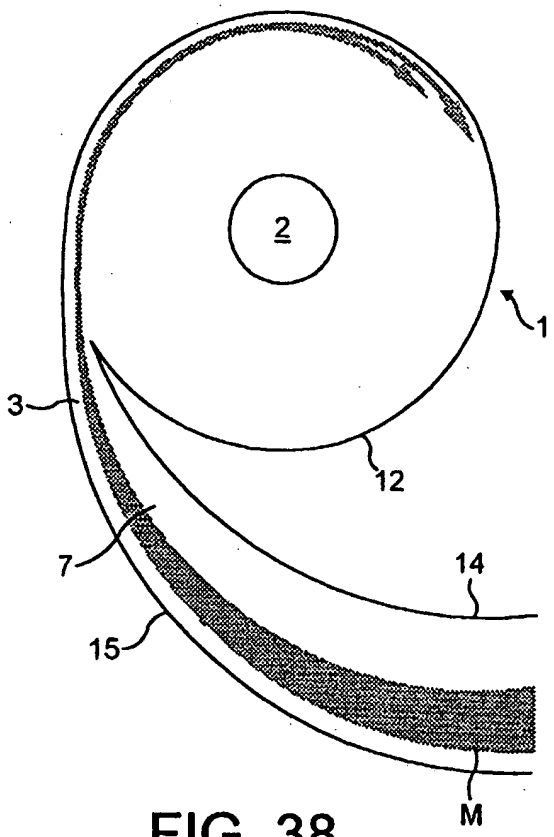

FIG. 38

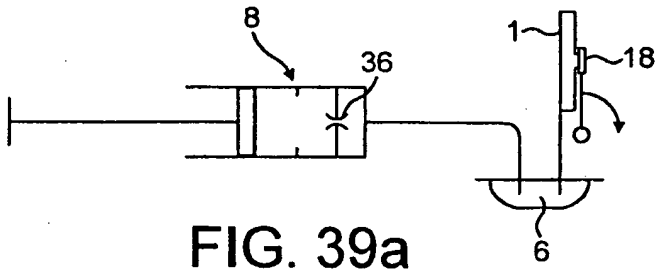

FIG. 39a

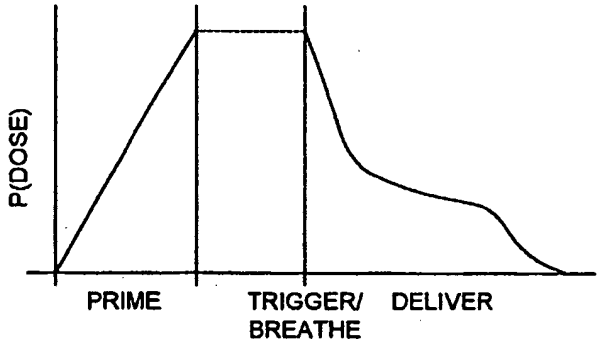

FIG. 39b

INTERNATIONAL SEARCH REPORT

Int[illegible]al Application No
PC[illegible]P 02/05185

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 404 871 A (GOODMAN DAVID E ET AL) 11 April 1995 (1995-04-11) column 19, line 14 -column 20, line 13; figure 2A ---	1-5, 12-16, 25,26,29
X	WO 00 29054 A (3M INNOVATIVE PROPERTIES CO) 25 May 2000 (2000-05-25) page 4, line 22 -page 5, line 8; figures 1-18 ---	1-5, 12-16, 25,26,29
A	WO 01 00262 A (CAMBRIDGE CONSULTANTS ;EASON STEPHEN WILLIAM (GB); HARMER QUENTIN) 4 January 2001 (2001-01-04) page 7, line 31 -page 8, line 21; figures 1,2 --- -/--	1-29

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 August 2002	10/09/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ceccarelli, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int. nal Application No
PC., .P 02/05185

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 524 613 A (SMEDLEY WILLIAM H ET AL) 11 June 1996 (1996-06-11) column 7, line 44 -column 8, line 26; figures 1,2,2A,2B	1-29
A	US 6 089 228 A (BURR JOHN D ET AL) 18 July 2000 (2000-07-18) the whole document	1-29

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/EP 02/05185

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 30-35
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int nal Application No
PCT/EP 02/05185

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Int inal Application No
PCT/EP 02/05185

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